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The multifaceted value of neuropsychological testing in daily neurosurgical practice

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Heterogeneous cognitive profiles in patients with glioma, meningioma and pituitary adenoma: The multifaceted value of neuropsychological testing in daily neurosurgical practice

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PART I

CHAPTER 1

General introduction and outline of the dissertation

Preface

Although primary brain tumors (PBT) account for a relatively small proportion of all forms of cancer,[1,2] they account for a disproportionately large share in cancer morbidity and mortality.[3] PBT pose a direct threat to all facets of human functioning;[4] emotional, physical, behavioral and cognitive. Still, clinical research has traditionally focused on the duration of (progression-free) survival.[5] As survival outcomes improved due to treatment advances, interest has shifted towards optimizing quality of survival.[6,7] Understanding and managing the symptomatology of PBT is a key aspect of this goal.

Cognitive dysfunction is one of the most common symptoms in both untreated and treated PBT patients.[8] Although potentially disruptive for the ability to function in various facets of daily life[9-11] and capacity for medical decision making,[12] it is under-recognized in clinical care.[13] Moreover, cognitive monitoring is often not a part of the standard care trajectory.[14] Several issues in current research may contribute to this discrepancy. First, there are caveats in our knowledge on the manifestation of cognitive dysfunction in PBT and relevant predictors on patient and disease level. Furthermore, the added value of routinely obtained cognitive measures for other purposes, such as early prognostic stratification and disease monitoring over time, is not always clear. Finally, research methodologies do not always match clinical questions and needs at hand, which creates a barrier for translation of scientific findings for care purposes. For example, studying patients' performances on separate cognitive domains does not correspond with the clinical need for understanding patients' functioning across domains (i.e., their "cognitive profiles").

The research comprising this dissertation centers around patients undergoing surgical resection of PBT at the Neurosurgery department of Elisabeth-Tweesteden Hospital, Tilburg, the Netherlands. The aims of this dissertation were to:

1) Contribute to our knowledge of the nature of cognitive (dys-)function, and relevant predictors, in benign and malignant PBT,
2) Illustrate the value of early and repeated postoperative cognitive measures for prognostic purposes in malignant PBT, and
3) Improve the alignment between research methodologies and question and needs in clinical care.

Cognitive functioning before and after surgical resection of three common classes of PBT (glioma, meningioma, pituitary adenoma) is investigated in Part II (**Chapters 2-5**). Part III comprises investigations of the value of postoperative cognitive status for early prognostic refinement (**Chapters 6)** and of longitudinal, personalized neuropsychological assessment for disease monitoring (**Chapter 7**) in glioma.

Primary brain tumors – epidemiology and burden on health care

The 2016 Global Burden of Disease Study reported that approximately 330.000 individuals are diagnosed with central nervous system (CNS) cancer on a yearly basis. This form of cancer is responsible for 6.9 to 8.3 million disability-adjusted life years (DALY), i.e., years of 'healthy' life lost due to morbidity and mortality.[15] CNS cancer also strongly affects patients' direct environment, as relatives who act as carers are at risk of compromised (mental) health.[16]

CNS cancers that specifically affect the brain can be broadly categorized into primary and secondary brain tumors. Primary brain tumors (PBT) comprise a heterogeneous class of tumors[17] that most often arise from glial tissue, the (glandular) pituitary, and, although strictly not part of the brain itself, the meninges. In contrast, secondary brain tumors arise when malignant cells from a primary tumor environment in another part of the body, most often lung or breast cancer or melanoma,[18] metastasize to the brain.

The most recent US Central Brain Tumor Registry[19] reported an average annual age-adjusted incidence rate for the major PBT classes - meningioma, glioma, pituitary adenoma - of approximately 8.56, 5.48, and 4.08 per 100.000 individuals respectively. Although the absolute incidence of PBT tumors increases with age, they rank higher in terms of the relative incidence among cancers within the young adult population (aged ≤ 39 years) as compared to the older adult population (>40 years). The incidence of PBT types further varies by factors such as sex and ethnic origin.[19]

PBT account for only ±2% of cancers.[17] However, they pose a great burden to health care,[20] not only because of the highly specialized, intensive, and often long-term multidisciplinary care that is required, but also due to their significant physical and psychological morbidity.[15,21] Monthly health care costs can be up to 20 times higher in PBT patients compared to demographically similar individuals without cancer.[22] Furthermore, estimates of objective burden for informal caregivers of PBT patients, measured in daily hours providing (custodial) care, are relatively high compared to other neurological and oncological illnesses.[20] Symptoms associated with this burden are associated higher health care utilization costs and decreased productivity for caregivers.[21]

Primary brain tumors – classification of major subtypes

The contemporary classification of PBT incorporates various histological (phenotypic) features and, for some tumor types, genetic characteristics.[23] About two-thirds of PBT are non-malignant tumors, that carry a favorable oncological prognosis, while malignant PBT account for about one-third of the total PBT population.[19]

Meningioma

The largest class of non-malignant tumors, making up approximately one third of the total PBT population,[1] constitutes WHO grade I (benign) and II (atypical) meningioma.

Meningioma are extra-axial tumors that likely originate from arachnoid meningothelial cells and can grow at various sites in the infra- and supratentorial compartments of the cranial cavity. Although strictly not malignant, atypical meningioma can show a tendency towards local invasion and recurrence after (subtotal) removal.[24,25] Diagnosis, grading and subtyping is currently primarily based on histological features. The role of genetic profiling, e.g, downregulation of genes on chromosome 14q,[26] for future diagnostics and treatment is being investigated.[27]

Meningioma are diagnosed about 2.5 times more often in women than men (incidence 4.5:100.000 vs 1.8:100.000).[28] The true prevalence of meningioma in the population is significantly higher than the number derived from diagnosed cases, as many cases remain undetected due to their asymptomatic nature. In a study by Vernooij and colleagues of incidental findings on MRI scans,[29] about 1.1% of female and 0.9% of male subjects harbored an asymptomatic meningioma. Extrapolating to the Dutch population, the prevalence would be 75.000 to 100.000 cases.[28]

Pituitary adenoma

Tumors growing from the anterior pituitary (i.e., pituitary adenoma) are officially recognized as neuroendocrine tumors. The vast majority of pituitary adenoma are non-malignant (<1% are classified as malignant), although up to 35% can show invasive features, such as infiltration of the sphenoid sinus.[30] As a group, pituitary adenoma are the second most common type of non-malignant PBT and make up 16% of the total PBT population.[17]

Anatomical classification can be based on radiological evidence, where the tumor can be confined to the sella (microadenomas, < 1cm), or extend above the sella (macroadenoma ≥1cm) with various degrees of extension and sellar destruction.[31] WHO classification of adenoma subtype currently adopts a designation that combines traditionally used features, including morphology and cellular hormonal content, with a transcription factor profile that differentiates between different cell lineages.[32] Major subtypes include somatotroph (growth hormone producing), lactotroph (prolactin producing), corticotroph (ACHT producing), gonadotroph (gonadal hormone producing), thyrotroph (TSH producing), plurihormonal (combinations) and null cell (no production of adenohypophyseal hormones) adenoma.[31,32]

Tumors with clinical endocrine activity detected in immunohistochemical analysis and serum hormone levels are historically referred to as functioning pituitary adenoma. Those that do not secrete hormones or below a clinically relevant level are referred to as non-functioning pituitary adenoma (NFPA, 14-54% of cases in varying series).[33] Characteristic of NFPA can be their relatively large size and extension beyond the sella through which they can damage and compress adjacent structures, including the optic chiasm (causing visual disturbances) and pituitary itself (causing hormonal deficiencies, ±37-85% of cases).[33]

Glioma

About 75% percent of *malignant* PBT comprise diffuse glioma. Their incidence in Europe lies around 6:100.000 individuals,[34] and approximately 1100 individuals are diagnosed in the Netherlands each year.[35]

The broad class of glioma comprises various tumors that share histological features with different types of glial cells, such as astrocytes (astrocytoma) and oligodendrocytes (oligodendroglioma). Histological grading takes into account the presence of nuclear atypia (WHO grade II, low grade glioma), increased cell proliferation (WHO grade III, anaplastic glioma), and microvascular proliferation and/or necrosis (WHO grade IV, glioblastoma). Higher tumor grade is related to more aggressive clinical behavior and poorer prognosis. Still, low grade glioma can be particularly disruptive for patients' lives, because their peak age is relatively low (35-44 years[36]) as compared to, for example, glioblastoma (>55 years).[37]

The most recent WHO classification of CNS tumors[23] combines the glioma's histological features with genetic markers that serve further diagnostic accuracy and prognostic stratification. It presented a major restructuring and introduced new entities based on the combination of these features. For example, a distinction could not be reliably made between primary (i.e., de novo) and secondary (i.e., progressed from a lower grade) glioblastoma based on histology alone, even though these two types proposedly derive from different neural precursor cells and differ with regards to survival duration. Isocitrate dehydrogenase gene 1 (IDH1) mutation is, however, a distinctive feature of secondary glioblastoma.[38] Another example of the added value of genetic subtyping for diagnostic purposes concerns combined loss of the short arm of chromosome 1 and long arm of chromosome 19 (i.e., 1p/19-codeletion). This feature distinguishes oligodendroglial from astrocytic glioma, thereby making diagnosis of mixed oligo-astrocytic tumors redundant under the new classification.[23] Genetic features can also be predictive of treatment response. For example, silencing of the O6-methylguanine-DNA methyltransferase [*MGMT*] gene is a known biomarker for response to temozolomide chemotherapy.[23]

Treatment and prognosis

Benign PBT

The threat of non-malignant tumors like meningioma and pituitary adenoma, and the reason for intervention, does not lie in their potential for invasive or aggressive growth. Rather, treatment is usually commenced due to the presence of clinical symptoms that result from increased intracranial pressure and/or mass effect that subsequently disrupt functioning of proximal structures and more distally located regions. Depending on the balance between risk and expected benefit, surgical resection is a preferred treatment of choice in these symptomatic tumors.[27,39] Removal of a meningioma or adenoma provides a definitive diagnosis (as tissue is obtained), and aims to relief symptoms and obtain optimal local disease control. Local control rates are generally high,[40] but depend on the presence of atypical or invasive features, the extent of resection and whether non-radical resection is followed by stereotactic radiotherapy or –surgery.[39,40]

Glioma

Like benign PBT, malignant PBT affect both local and global brain function and can increase intracranial pressure. However, these tumors pose a major concern because of their infiltrative growth that disables complete surgical resection, their location behind the blood-brain-barrier that hampers delivery of systemic therapeutic agents, and the immune-suppressive nature of the tumor microenvironment.[2,41]

Treatment for diffuse glioma is not curative, as even low grade glioma progress toward higher malignancy over time.[42] Surgical resection is the preferred first step in a multidisciplinary therapeutic approach for glioma as seen from an oncological viewpoint. Still, surgical decision making depends on tumor resectability and needs to balance risk (e.g., loss of function) with expected oncological benefit.[43] Depending on tumor features as well as patient characteristics, such as functional status (i.e., the degree of functional impairment) and age, adjuvant treatment strategies can significantly prolong survival[44] and improve or maintain quality of life.[3]

The clinical outcome of glioma is highly variable,[45] as illustrated by median overall survival duration of only 13 months in patients with IDH1-wildtype glioblastoma (WHO grade IV[46]) up to 157 months in 1p-19q co-deleted oligodendroglioma (WHO grade II).[47] Prognosis appears to be tied more closely to the tumor's genetic profile than its morphology,[46,48] although histological grading remains relevant for prognostic stratification. Alongside tumor characteristics and treatment, several clinical prognostic indicators throughout the care trajectory have shown additional value in predicting survival outcome. Some of the major clinical predictors include extent of tumor resection,[43] which is partly related to tumor location, and perioperative functional status (Karnofsky Performance Status, KPS).[49,50] Age may also be a prognostic indicator,[51] but its influence is not uncontested, given its relationship with glioma subtype[37,45] and (adjuvant) treatment decisions,[52] as well as non-significant results in patients over 60 years of age.[53]

Heterogeneous and burdensome symptomatology

PBT symptomatology is very heterogeneous,[54] as it can involve emotional, behavioral, physical and/or cognitive dysfunction. Moreover, multiple, different symptoms are often present at the same time. A study by Armstrong and colleagues[55] found that over 50% of PBT patients reported more than ten concurrent symptoms. In the same study, the majority of symptoms significantly influenced clinically evaluated Karnofsky Performance Status, and 25% of patients reported themselves that symptoms interfered with their daily activities.

Symptom clusters are often already present at time of diagnosis[56] as a result of mass effect and/or parenchymal infiltration with subsequent damage to neural tissue. At this time, symptomatology is significantly related to tumor characteristics. For example, low grade glioma most often present with epilepsy (>50% of cases), [57] whereas focal neurologic deficits and cognitive dysfunction occur more frequently with glioblastoma.[57,58] Tumor location can also influence pre-treatment symptoms; e.g., meningioma located at the skull base often induce specific cranial nerve deficits, while those growing at the convexity frequently present with headaches and cognitive dysfunction.[59] Larger tumor volume and peritumoral edema are also predictors of (the degree of) pre-treatment symptomatology.[60,61] Symptoms that patients report most frequently, irrespective of lesion characteristics and treatment status, tend to be non-specific in nature, and include fatigue and sleep disturbance.[55]

Although symptom relief is an important therapeutic aim, some symptoms may linger or be exacerbated over the course of and after completion of treatment. Moreover, adjuvant modalities (e.g., chemotherapy and radiotherapy) can also elicit new deficits,[55,62] proposedly due to cellular toxicity and loss that results from oxidative stress and DNA damage[63] and suppression of progenitor cell proliferation.[64,65]

Cognitive functioning in patients with PBT

Despite the different pathophysiology, both benign and malignant PBT can induce disruption of cognitive functioning. In fact, cognitive symptoms are among the most common symptoms found in the PBT population.[54] Cognitive functioning is generally understood to cover 4 main functional classes, including receptive functions, memory and learning, mental (re-)organization and expressive functions. Within each class, discrete functions are identified. It is important to note that these classes are primarily distinguished on a conceptual level, as in practice they reflect interconnected facets.[66]

Cognitive functioning can be measured in several ways. A broad distinction can be made between “objective measurement” - i.e., measuring one’s performance on tests that tap into cognitive domains, such as memory, processing speed, and executive function - and “subjective measurement” - i.e., by means of self-report or proxy report that indicates one’s experience of cognitive functioning,[54] such as the ability to remember names or navigate in new or familiar environments. Cognitive impairment on tests, which is one of the measures of interest in this thesis, is reportedly present in the majority of PBT patients.[61,67,68] This means that these patients perform below a clinically established threshold of dysfunction on one or more neuropsychological tests, for example, below the 6.7th percentile based on data from a (healthy) normative sample. There may be an additional proportion of patients suffering milder cases of disturbed cognitive functioning.[69] Alongside its particularly high prevalence, cognitive dysfunction is also reported as a primary source of burden by caregivers.[70]

Developments in and recent insights from research into cognitive functioning

Studied outcomes in PBT have long been restricted to survival and overt neurological deficits, such as motor function. As duration of survival improved parallel to advances in anti-tumor treatment, a focus on quality of survival and functioning during stable disease, and thus cognitive functioning, became more important.[6] Still, a conceptual review by Wefel and colleagues published in 2004[71] raised several methodological issues in published literature on cognition in PBT patients at the time. These issues included heterogeneity in cognitive assessments and patient samples between studies, lacking control groups, and the often retrospective nature of investigations. Over the past 15 years, multiple valuable insights have been generated from the surge in quality studies. These insights have confirmed the inadequacy of a singular focus on neurological status or survival in research and care. [68,72-80]

Possible similarities and differences in cognitive dysfunction between PBT types

One important understanding we can derive from recent research is that some cognitive domains, such as executive functioning, may be particularly vulnerable to burden across tumor types.[14,68,73,78] At the same time, susceptibility to disruption of other cognitive functions, such as memory and psychomotor function, may differ between diagnoses.[75,78,81] It is also argued that the *severity* of dysfunction is (partly) different between diagnoses, where meningioma and low grade (WHO II) glioma are suggested to invoke milder disturbances than high grade glioma(WHO III/IV), [68,73] possibly as a result of a less disruptive growth pattern, more opportunity for compensation due to lower lesion momentum, and less aggressive treatment. Taken together, it appears that there may be some overlapping, but also some dissimilar profiles of cognitive functioning present between PBT populations. At the same time, the precise nature of these cognitive profiles is currently not clear.

Predictors of dysfunction

A second domain where substantial progress has been made is the investigation of factors that influence cognitive (dys-)function. The fact that factors on various levels - patient, disease, and treatment - can be relevant is now undisputed. Effects of some characteristics, such as age,[82,83] comorbidity,[72] and the presence of epilepsy, [84-86] appear to span across PBT populations. Many factors may, however, determine cognitive fitness in a disease-specific way, either because *they are confined to a specific tumor type* (e.g., high lesion momentum and systemic treatment specific to diffuse glioma,[87], and growth in the sellar region specific to meningioma[88] and pituitary adenoma) or because *their effects appear disparate across tumor types* (e.g., the influence of the affected [88-90] hemisphere on cognition may differ). Despite our knowledge on factors that affect cognition on a population level, it remains particularly challenging to predicting cognition for individual patients at any phase of the disease.Moreover, there is a substantial number of patient (e.g., germline genetic polymorphisms) and disease (e.g., hormonal dysfunction) characteristics of which the effects on cognition in the PBT population are still unclear due to a paucity of research.

Advances in the approach to studying cognition

Significant insights have also been presented on best practices for studying cognition, in particular the use of individual patient level in addition to group (mean) level approaches.[91] As a result of thorough comparisons of results generated from both approaches, we now know that investigating only group performances is not appropriate for individual patients in clinical care,[92] because the variability in cognitive performances and their trajectories of individual patients is not captured in group-level results.[69,92] For example, within a patient sample that, based on their average group score, deviates only mildly from a normative sample, there may be a subgroup of individual patients with actual cognitive impairment. Similarly, for cognitive trajectories over time, group findings may provide intuitive results in reporting overall improvement after tumor resection. However, they do not indicate if there were individual patients who showed decline. The importance of incorporating individual level results alongside group results is now recommended as standard practice in clinical research.[92]

The potential value of cognition as predictive measure

Finally, measurement of cognitive function has been shown to have a multifaceted value for clinical care, as it relates to various other domains of PBT patients' daily functioning, such as (medical) decision making capability,[93] time management and coping with physical demands at work,[94]quality of life, [95] interpersonal functioning,[94,96] and functional independence.[97] Moreover, early postoperative cognitive impairment - before start of adjuvant treatment - even appears to predict poorer survival outcome[98] and decline in cognitive functioning over time appears to be related to recurrent tumor activity[99-101] in high grade glioma patients. A similar phenomenon has been observed in other neurological afflictions with a progressive nature,[102,103] indicating that cognition may be useful as an additional, non-invasive proxy measure for (recurrent) disease activity.[101]

Opportunities in research on cognitive functioning in patients with PBT

To this day, cognitive deficits are often overlooked or underestimated in clinical practice for various reasons.[13,54] The more covert nature of cognitive deficits can partly contribute, as it makes them harder to observe during a limited clinical evaluation than other symptoms. Moreover, patients' reporting of subjective experience of their daily cognitive functioning is by itself not a sufficient indicator of the actual objective level of functioning as measured with tests.[104] Objective cognitive evaluation requires separate and sometimes lengthy assessments that can be expensive and difficult to integrate in regular care trajectories,[54] especially as the benefits of obtaining cognitive measures for clinical purposes as well as strategies for efficient testing are not always clear for clinical staff. In the burgeoning of quality research and insights on cognition in PBT, several questions and issues may still be addressed as we aim to solidify cognitive monitoring as an integral part of disease management:

First, the level of empirical evidence and the methodological quality of research differs between different tumor categories. Relative to meningioma and glioma, the literature on pituitary adenoma, for example, remains methodologically heterogeneous,[105] and there is a lack of prospective investigations of cognition surrounding surgical intervention.[75] This variance in quantity and quality of empirical evidence within the PBT population, may subsequently lead to differences in the quality of care provided. Moreover, as mentioned, our understanding of the influence of a number of patient and disease characteristics also remains limited to date due to a paucity in studies. For example, germ-line genetic determinants of cognitive functioning, such as allelic variations of the APOE gene, are relatively scarcely researched in PBT patients,[106] even though they have been established predictors of cognitive outcomes in healthy adults [107,108] and patients treated for non-CNS cancer.[109]

Second, despite the addition of individual level analyses, most current approaches to cognitive profiling in PBT still do not allow us to adequately understand the heterogeneity in cognitive functioning, because each cognitive test or domain is investigated separately from the others. This approach disregards a part of the nature of cognition, namely that cognitive domains show differential interrelations,[66,110] similar to the neural networks that underlie cognitive functions seem to do.[66,111,112] For example, problems with information processing speed have been shown to influence specific complex functions, [113] such as task switching.[114] This relationship is proposedly a function of their shared mechanisms, including stimulus perception, decision making and planning, and performance evaluation.[115] The association between information processing speed and memory performance appears less strong, indicating that these domains may function more distinctly.[114] By approaching them separately, we cannot retrieve insights into which *patterns* exist in performances *across cognitive tests or domains*. This subsequently leaves unknown what cognitive profiles exist in this apparent cognitive heterogeneity.. Investigations of covert patterns in patients' performances across neuropsychological tests can provide new insights that may be more true to the nature of cognition and its evaluation in clinical practice.

The *third* issue concerns the prognostic value of cognitive measures and how this may fit in clinical practice. Although advances have been made in exploring the prognostic value of early postoperative cognitive status,[98,116] we do not know whether poor cognitive status measured at a regular clinical follow up during early adjuvant treatment can be used as an early prognostic indicator alongside known clinical factors. Moreover, the effect of early cognitive status on survival outcome is reported with hazard or odds ratio's. These statisticsprovide inform us about which patients are more likely to experience an event like progression or death during a follow up period, but not it does not directly provide knowledge about the difference in *time until this occurs*. In fact, for malignant gliomathat inevitably lead to progression and death, the latter is especially important. A translation of the effects of cognition into differences in survival duration is more easily interpretable for clinicians.

Cognitive change may also have value in disease monitoring, as it may reflect tumor activity over time.[101] Still, capturing those cognitive functions that are most sensitive to tumor activity remains difficult, as they may differ between individual patients.[99] The question of how to capture those domains that are sensitive to changes in tumor activity in individual patients is still open, as well as how their assessment can be made efficient and integrated into clinical care.

Goal and outline of this dissertation

The research in this dissertation focuses on *three objectives*:

1) Contributing to our understanding of cognitive (dys-)function and relevant predictors thereof in patients with adenoma, meningioma and glioma (addressed in Part II),
2) Illustrating the multifarious value of routinely obtained data on cognitive functioning for clinical practice, specifically for early prognostic stratification and longitudinal disease monitoring of patients with high grade glioma, (addressed in Part III), and
3) Improving the alignment of methodologies applied in research and questions and needs in the clinical setting, such as the interpretability of results and potential for integration in care (addressed in Part II and Part III).

By addressing these objectives, this dissertation aims to contribute to improvement of patient informing, and ultimately, facilitation of personalized monitoring, shared decision making, and targeted intervention for cognitive symptomatology.

Part II of this thesis comprises Chapters 2-5. In **Chapter 2**, we investigated the course of cognitive functioning of patients with non-functioning pituitary adenoma undergoing endoscopic transsphenoidal resection on group- and individual level to contribute to our knowledge of the peri-surgical trajectory and tumor-related predictors of cognition in this relatively understudied population. In **Chapter 3**, we examined the association between APOE genotypic variation, in particular carrier status of the APOE ε4 allele, and the longitudinal course of cognitive functioning in meningioma and glioma patients from pre- to 12 months post-surgical follow-up. **Chapters 4** and **5** aimed to elucidate and predict currently unknown latent profiles of cognitive impairment across different neuropsychological tests in patients with diffuse glioma and meningioma.

Part III comprises Chapters 6 and 7. **Chapter 6** addresses the relationship between cognitive impairment during early adjuvant treatment and survival duration in patients with glioblastoma using a clinically intuitive statistical approach, in order to establish whether impairment in this phase can be used as a prognostic indicator. In **Chapter 7** we investigated whether brief, longitudinal, personalized cognitive assessment could predict disease progression in patients with anaplastic astrocytoma and glioblastoma, in order to explore its potential as a non-invasive addition to regular disease monitoring. **Chapter 8** provides a general discussion of the findings of this dissertation and recommendations for clinical and future research practices.

REFERENCES

1. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2011–2015. *Neuro-oncology.* 2018;20(suppl_4):iv1-iv86.
2. Aldape K, Brindle KM, Chesler L, et al. Challenges to curing primary brain tumours. *Nat Rev Clin Oncol.* 2019;16(8):509-520.
3. Taphoorn MJB, Sizoo EM, Bottomley A. Review on quality of life issues in patients with primary brain tumors. O*ncologist.* 2010;15(6):618-626.
4. Keir ST, Calhoun-Eagan RD, Swartz JJ, Saleh OA, Friedman HS. Screening for distress in patients with brain cancer using the NCCN’s rapid screening measure. *Psychooncol.* 2008;17(6):621-625.
5. Fox SW, Lyon D, Farace E. Symptom clusters in patients with high-grade glioma. *J Nurs Scholarsh.* 2007;39(1):61-67.
6. Gehring K, Sitskoorn MM, Aaronson NK, Taphoorn MJB. Interventions for cognitive deficits in adults with brain tumours. *Lancet Neurol.* 2008;7(6):548-560.
7. Duffau H. Hodotopy, neuroplasticity and diffuse gliomas. *Neurochirurgie.* 2017;63(3):259-265.
8. Noll KR, Bradshaw ME, Parsons MW, Dawson EL, Rexer J, Wefel JS. Monitoring of Neurocognitive Function in the Care of Patients with Brain Tumors. *Curr Treat Opt Neurol.* 2019;21(7):33.
9. Duijts SFA, van der Beek AJ, Boelhouwer IG, Schagen SB. Cancer-related cognitive impairment and patients’ ability to work: a current perspective. *Curr Opin Support Palliat Care.* 2017;11(1): 19-23.
10. Aerts H, Van Vrekhem T, Stas L, Marinazzo D. The interplay between emotion regulation, emotional well-being, and cognitive functioning in brain tumor patients and their caregivers: an exploratory study. *Psychooncol.* 2019;28(10):2068-2075.
11. Klein M, Taphoorn MJB, Heimans JJ, et al. Neurobehavioral status and health-related quality of life in newly diagnosed high-grade glioma patients. *J Clin Oncol.* 2001;19(20):4037-4047.
12. Lee J, Hall RCW. The impact of gliomas on cognition and capacity. *J Am Acad Psychiatry Law.* 2019:JAAPL.003841-003819.
13. Bernstein M. Under-recognized mental incapacity in brain tumour patients. *Nat Rev Neurol.* 2014;10(9):487-488.
14. Talacchi A, Santini B, Savazzi S, Gerosa M. Cognitive effects of tumour and surgical treatment in glioma patients. *J Neurooncol.* 2011;103(3):541-549.
15. Patel AP, Fisher JL, Nichols E, et al. Global, regional, and national burden of brain and other CNS cancer, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2019;18(4):376-393.
16. Boele FW, Heimans JJ, Aaronson NK, et al. Health-related quality of life of significant others of patients with malignant CNS versus non-CNS tumors: a comparative study. *J Neurooncol.* 2013;115(1):87-94.
17. Lapointe S, Perry A, Butowski NA. Primary brain tumours in adults. *Lancet.* 2018;392(10145): 432-446.
18. Rahmathulla G, Toms SA, Weil RJ. The molecular biology of brain metastasis. *J Oncol.* 2012;2012:723541.

19. Ostrom QT, Cioffi G, Gittleman H, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012–2016. *Neuro-oncology.* 2019;21(Supplement_5):v1-v100.

20. Bayen E, Laigle-Donadey F, Prouté M, Hoang-Xuan K, Joël M-E, Delattre J-Y. The multidimensional burden of informal caregivers in primary malignant brain tumor. *Supp Care Cancer.* 2017;25(1):245-253.

21. Boele FW, Meads D, Jansen F, et al. Healthcare utilization and productivity loss in glioma patients and family caregivers: the impact of treatable psychological symptoms. *J Neurooncol.* 2020;147(2):485-494.

22. Kutikova L, Bowman L, Chang S, Long SR, Thornton DE, Crown WH. Utilization and cost of health care services associated with primary malignant brain tumors in the United States. *J neurooncol.* 2007;81(1):61-65.

23. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol.* 2016;131(6):803-820.

24. Shakir SI, Souhami L, Petrecca K, et al. Prognostic factors for progression in atypical meningioma. *J Neurosurg*. 2018;129(5):1240.

25. Wiemels J, Wrensch M, Claus EB. Epidemiology and etiology of meningioma. *J Neurooncol.* 2010;99(3):307-314.

26. Riemenschneider MJ, Perry A, Reifenberger G. Histological classification and molecular genetics of meningiomas. *Lancet Neurol.* 2006;5(12):1045-1054.

27. Goldbrunner R, Minniti G, Preusser M, et al. EANO guidelines for the diagnosis and treatment of meningiomas. *Lancet Oncol.* 2016;17(9):e383-e391.

28. Landelijke Werkgroep Neuro-Oncologie. *Richtlijn Meningeoom.* 2015.

29. Vernooij MW, Ikram MA, Tanghe HL, et al. Incidental findings on brain MRI in the general population. *N Engl J Med.* 2007;357(18):1821-1828.

30. Hansen TM, Batra S, Lim M, et al. Invasive adenoma and pituitary carcinoma: a SEER database analysis. *Neurosurg rev.* 2014;37(2):279-286.

31. Mete O, Lopes MB. Overview of the 2017 WHO Classification of pituitary tumors. *Endocr Pathol.* 2017;28(3):228-243.

32. Lopes MBS. The 2017 World Health Organization classification of tumors of the pituitary gland: a summary. *Acta Neuropathol.* 2017;134(4):521-535.

33. Ntali G, Wass JA. Epidemiology, clinical presentation and diagnosis of non-functioning pituitary adenomas. *Pituitary.* 2018;21(2):111-118.

34. Landelijke Werkgroep Neuro-Oncologie. *Richtlijn Gliomen.* 2015.

35. Landelijke Werkgroep Neuro-Oncologie. *Dutch Brain Tumor Registry (DBTR) 2014-2017: Glioomzorg in Nederland.* 2019. https://lwno.nl/media/1050/rapportage-glioomzorg-dbtr-2014-2017.pdf

36. Oberheim Bush NA, Chang S. Treatment strategies for low-grade glioma in adults. *J Oncol Pract.* 2016;12(12):1235-1241.

37. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. *N Engl J Med.* 2009;360(8):765-773.

38. Ohgaki H, Kleihues P. The definition of primary and secondary glioblastoma. *Clin Cancer Res.* 2013;19(4):764.

39. Philippe C, Alexandre D, Olaf MD. Use of radiotherapy after pituitary surgery for non-functioning pituitary adenomas. *Eur J Endocrinol.* 2019;181(1):D1-D13.

40. Rogers L, Barani I, Chamberlain M, et al. Meningiomas: knowledge base, treatment outcomes, and uncertainties. A RANO review. *J Neurosurg.* 2015;122(1):4-23.

41. Quail DF, Joyce JA. The microenvironmental landscape of brain tumors. *Cancer Cell.* 2017;31(3):326-341.

42. Delgado-López PD, Corrales-García EM, Martino J, Lastra-Aras E, Dueñas-Polo MT. Diffuse low-grade glioma: a review on the new molecular classification, natural history and current management strategies. *Clin Transl Oncol.* 2017;19(8):931-944.

43. Thon N, Tonn J-C, Kreth F-W. The surgical perspective in precision treatment of diffuse gliomas. *Onco Targets Ther.* 2019;12:1497-1508.

44. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. *New Engl J Med.* 2005;352(10):987-996.

45. Molinaro AM, Taylor JW, Wiencke JK, Wrensch MR. Genetic and molecular epidemiology of adult diffuse glioma. *Nat Rev Neurol.* 2019;15(7):405-417.

46. Hartmann C, Hentschel B, Wick W, et al. Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas. *Acta Neuropathol.* 2010;120(6):707-718.

47. van den Bent MJ, Brandes AA, Taphoorn MJB, et al. Adjuvant Procarbazine, Lomustine, and Vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol.* 2012;31(3):344-350.

48. Buckner J, Giannini C, Eckel-Passow J, et al. Management of diffuse low-grade gliomas in adults — use of molecular diagnostics. *Nat Rev Neurol.* 2017;13(6):340-351.

49. Chambless LB, Kistka HM, Parker SL, Hassam-Malani L, McGirt MJ, Thompson RC. The relative value of postoperative versus preoperative Karnofsky Performance Scale scores as a predictor of survival after surgical resection of glioblastoma multiforme. *J Neurooncol.* 2015;121(2):359-364.

50. Jungk C, Warta R, Mock A, et al. Location-dependent patient outcome and recurrence patterns in IDH1-wildtype glioblastoma. *Cancers (Basel).* 2019;11(1):122.

51. Gorlia T, van den Bent MJ, Hegi ME, et al. Nomograms for predicting survival of patients with newly diagnosed glioblastoma: prognostic factor analysis of EORTC and NCIC trial 26981-22981/CE.3. *Lancet Oncol.* 2008;9(1):29-38.

52. Gately L, Collins A, Murphy M, Dowling A. Age alone is not a predictor for survival in glioblastoma. *J Neurooncol.* 2016;129(3):479-485.

53. Morshed RA, Han SJ, Hervey-Jumper SL, et al. Molecular features and clinical outcomes in surgically treated low-grade diffuse gliomas in patients over the age of 60. *J Neurooncol.* 2019;141(2):383-391.

54. Day J, Gillespie DC, Rooney AG, et al. Neurocognitive deficits and neurocognitive rehabilitation in adult brain tumors. *Curr Treat Opt Neurol.* 2016;18(5):22.

55. Armstrong TS, Vera-Bolanos E, Acquaye AA, Gilbert MR, Ladha H, Mendoza T. The symptom burden of primary brain tumors: evidence for a core set of tumor- and treatment-related symptoms. *Neuro-oncology.* 2016;18(2):252-260.

56. Armstrong TS, Cohen MZ, Eriksen LR, Hickey JV. Symptom clusters in oncology patients and implications for symptom research in people with primary brain tumors. *J Nurs Scholarsh.* 2004;36(3):197-206.

57. Rasmussen BK, Hansen S, Laursen RJ, et al. Epidemiology of glioma: clinical characteristics, symptoms, and predictors of glioma patients grade I–IV in the the Danish Neuro-Oncology Registry. *J Neurooncol.* 2017;135(3):571-579.

58. Hanif F, Muzaffar K, Perveen K, Malhi SM, Simjee SU. Glioblastoma Multiforme: a review of its epidemiology and pathogenesis through clinical presentation and treatment. *Asian Pac J Cancer Prev.* 2017;18(1):3-9.

59. Wu A, Garcia MA, Magill ST, et al. Presenting symptoms and prognostic factors for symptomatic outcomes following resection of meningioma. *World Neurosurg.* 2018;111:e149-e159.

60. Tucha O, Smely C, Preier M, Lange KW. Cognitive deficits before treatment among patients with brain tumors. *Neurosurg.* 2000;47(2):324-333; discussion 333-324.

61. Bommakanti K, Somayajula S, Suvarna A, et al. Pre-operative and post-operative cognitive deficits in patients with supratentorial meningiomas. *Clin Neurol Neurosurg.* 2016;143:150-158.

62. Armstrong CL. Late-Delayed Effects of Radiation Therapy. In: Kreutzer JS, DeLuca J, Caplan B, eds. *Encyclopedia of Clinical Neuropsychology.* New York, NY: Springer New York; 2011:1429-1431.

63. Kaiser J, Bledowski C, Dietrich J. Neural correlates of chemotherapy-related cognitive impairment. *Cortex.* 2014;54:33-50.

64. Makale MT, McDonald CR, Hattangadi-Gluth JA, Kesari S. Mechanisms of radiotherapy-associated cognitive disability in patients with brain tumours. *Nat Rev Neurol.* 2017;13(1):52-64.

65. Ahles TA. Brain vulnerability to chemotherapy toxicities. *Psychooncol.* 2012;21(11):1141-1148.

66. Lezak MD, Howieson DB, Bigler ED, Tranel D. *Neuropsychological assessment, 5th ed.* New York, NY, US: Oxford University Press; 2012.

67. Meskal I, Gehring K, van der Linden SD, Rutten G-JM, Sitskoorn MM. Cognitive improvement in meningioma patients after surgery: clinical relevance of computerized testing. *J Neurooncol.* 2015;121(3):617-625.

68. van Kessel E, Baumfalk AE, van Zandvoort MJE, Robe PA, Snijders TJ. Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a systematic review of neurocognitive functioning prior to anti-tumor treatment. *J Neurooncol.* 2017;134(1):9-18.

69. van Loenen IS, Rijnen SJM, Bruijn J, Rutten GM, Gehring K, Sitskoorn MM. Group Changes in Cognitive Performance After Surgery Mask Changes in Individual Patients with Glioblastoma. *World Neurosurg.* 2018;117:e172-e179.

70. Locke DE, Cerhan JH, Wu W, et al. Cognitive rehabilitation and problem-solving to improve quality of life of patients with primary brain tumors: a pilot study. *J Support Oncol.* 2008;6(8):383-391.

71. Wefel JS, Kayl AE, Meyers CA. Neuropsychological dysfunction associated with cancer and cancer therapies: a conceptual review of an emerging target. *Br J Cancer.* 2004;90(9):1691-1696.

72. Taphoorn MJB, Klein M. Cognitive deficits in adult patients with brain tumours. *Lancet Neurol.* 2004;3(3):159-168.

73. Meskal I, Gehring K, Rutten G-JM, Sitskoorn MM. Cognitive functioning in meningioma patients: a systematic review. *J Neurooncol.* 2016;128(2):195-205.

74. Wefel JS, Noll KR, Scheurer ME. Neurocognitive functioning and genetic variation in patients with primary brain tumours. *Lancet Oncol.* 2016;17(3):e97-e108.

75. Alsumali A, Cote DJ, Regestein QR, et al. The impact of transsphenoidal surgery on neurocognitive function: A systematic review. *J Clin Neurosci.* 2017;42:1-6.

76. Ali FS, Hussain MR, Gutiérrez C, et al. Cognitive disability in adult patients with brain tumors. *Cancer Treat Rev.* 2018;65:33-40.

77. Jacob J, Durand T, Feuvret L, et al. Cognitive impairment and morphological changes after radiation therapy in brain tumors: A review. *Radiother Oncol.* 2018;128(2):221-228.

78. Sinha R, Stephenson JM, Price SJ. A systematic review of cognitive function in patients with glioblastoma undergoing surgery. *Neurooncol Pract.* 2019.

79. Amidei C. Symptom-based interventions to promote quality survivorship. *Neuro-oncology.* 2018;20(suppl_7):vii27-vii39.

80. Pertz M, Popkirov S, Schlegel U, Thoma P. Research on cognitive and sociocognitive functions in patients with brain tumours: a bibliometric analysis and visualization of the scientific landscape. *Neurol Sci.* 2020;41(6):1437-1449.

81. Tucha O, Smely C, Preier M, Becker G, Paul GM, Lange KW. Preoperative and postoperative cognitive functioning in patients with frontal meningiomas. *J Neurosurg.* 2003;98(1):21-31.

82. Mussig K, Leyhe T, Besemer B, et al. Younger age is a good predictor of better executive function after surgery for pituitary adenoma in adults. *J Int Neuropsych Soc.* 2009;15(5):803-806.

83. Rijnen SJM, Meskal I, Bakker M, et al. Cognitive outcomes in meningioma patients undergoing surgery: individual changes over time and predictors of late cognitive functioning. *Neuro-oncology.* 2019;21(7):911-922.

84. Dijkstra M, van Nieuwenhuizen D, Stalpers LJA, et al. Late neurocognitive sequelae in patients with WHO grade I meningioma. *J Neurol, Neurosurg Psychiatry.* 2009;80(8):910.

85. Bouwen BLJ, Pieterman KJ, Smits M, Dirven CMF, Gao Z, Vincent AJPE. The impacts of tumor and tumor associated epilepsy on subcortical brain structures and long distance connectivity in patients With low grade glioma. *Front Neurol.* 2018;9(1004).

86. Klein M, Engelberts NHJ, van der Ploeg HM, et al. Epilepsy in low-grade gliomas: The impact on cognitive function and quality of life. *Ann Neurol.* 2003;54(4):514-520.

87. Derks J, Kulik S, Wesseling P, et al. Understanding cognitive functioning in glioma patients: The relevance of IDH-mutation status and functional connectivity. *Brain and Behavior.* 2019;9.

88. Liouta E, Koutsarnakis C, Liakos F, Stranjalis G. Effects of intracranial meningioma location, size, and surgery on neurocognitive functions: a 3-year prospective study. *J Neurosurg.* 2016;124(6):1578-1584.

89. Habets EJJ, Kloet A, Walchenbach R, Vecht CJ, Klein M, Taphoorn MJB. Tumour and surgery effects on cognitive functioning in high-grade glioma patients. *Acta Neurochir.* 2014;156(8):1451-1459.

1

90. Hendriks EJ, Habets EJJ, Taphoorn MJB, et al. Linking late cognitive outcome with glioma surgery location using resection cavity maps. *Hum Brain Mapp.* 2018;39(5):2064-2074.

91. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol.* 2011;12(7):703-708.

92. Habets EJJ. *Neurocognitive functioning and health-related quality of life in patients with brain tumors* (dissertation). The Netherlands: Department of Neurology, Leiden University Medical Centre; 2020.

93. Triebel KL, Martin RC, Nabors LB, Marson DC. Medical decision-making capacity in patients with malignant glioma. *Neurology.* 2009;73(24):2086.

94. Nugent BD, Weimer J, Choi CJ, et al. Work productivity and neuropsychological function in persons with skull base tumors. *Neurooncol Pract.* 2014;1(3):106-113.

95. Giovagnoli AR, Silvani A, Colombo E, Boiardi A. Facets and determinants of quality of life in patients with recurrent high grade glioma. *J Neurol Neurosurg Psychiatry.* 2005;76(4):562-568.

96. Giovagnoli AR. Investigation of cognitive impairments in people with brain tumors. *J Neurooncol.* 2012;108(2):277-283.

97. Noll KR, Bradshaw ME, Wefel JS, Weinberg JS. Neurocognitive functioning is associated with functional independence in newly diagnosed patients with temporal lobe glioma. *Neurooncol Pract.* 2017;5(3):184-193.

98. Johnson DR, Sawyer AM, Meyers CA, O'Neill BP, Wefel JS. Early measures of cognitive function predict survival in patients with newly diagnosed glioblastoma. *Neuro-oncology.* 2012;14(6):808-816.

99. Armstrong CL, Goldstein B, Shera D, Ledakis GE, Tallent EM. The predictive value of longitudinal neuropsychologic assessment in the early detection of brain tumor recurrence. *Cancer.* 2003;97(3):649-656.

100. Meyers CA, Hess KR. Multifaceted end points in brain tumor clinical trials: cognitive deterioration precedes MRI progression. *Neuro-oncology.* 2003;5(2):89-95.

101. Zarino B, Di Cristofori A, Fornara GA, et al. Long-term follow-up of neuropsychological functions in patients with high grade gliomas: can cognitive status predict patient's outcome after surgery? *Acta Neurochirurgica.* 2020;162(4):803-812.

102. Moccia M, Lanzillo R, Palladino R, et al. Cognitive impairment at diagnosis predicts 10-year multiple sclerosis progression. *Mult Scler.* 2015;22(5):659-667.

103. Dujardin K, Defebvre L, Duhamel A, et al. Cognitive and SPECT characteristics predict progression of Parkinson's disease in newly diagnosed patients. *J Neurol.* 2004;251(11):1383-1392.

104. van Lonkhuizen PJC, Rijnen SJM, van der Linden SD, Rutten GM, Gehring K, Sitskoorn MM. Subjective cognitive functioning in patients with a meningioma: Its course and association with objective cognitive functioning and psychological symptoms. *Psychooncol.* 2019;28(8):1654-1662.

105. Pertichetti M, Serioli S, Belotti F, et al. Pituitary adenomas and neuropsychological status: a systematic literature review. *Neurosurg Rev.* 2019.

106. Correa DD, Satagopan J, Martin A, et al. Genetic variants and cognitive functions in patients with brain tumors. *Neuro-oncology.* 2019;21(10):1297-1309.

107. Chen CJ, Chen CC, Wu D, et al. Effects of the APOE ε4 Allele on Functional MRI during N-Back Working Memory Tasks in Healthy Middle-Aged Adults. *Am J Neuroradiol.* 2013;34(6):1197.

108. Rawle MJ, Davis D, Bendayan R, Wong A, Kuh D, Richards M. Apolipoprotein-E (Apoe) ε4 and cognitive decline over the adult life course. *Transl Psychiatry.* 2018;8(1):18.

109. Ahles TA, Saykin AJ, Noll WW, et al. The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. *Psychooncol.* 2003;12(6):612-619.

110. Perbal S, Couillet J, Azouvi P, Pouthas V. Relationships between time estimation, memory, attention, and processing speed in patients with severe traumatic brain injury. *Neuropsychologia.* 2003;41(12):1599-1610.

111. Ridderinkhof KR, van den Wildenberg WPM, Segalowitz SJ, Carter CS. Neurocognitive mechanisms of cognitive control: The role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. *Brain Cog.* 2004;56(2):129-140.

112. Vallesi A, McIntosh AR, Crescentini C, Stuss DT. fMRI investigation of speed–accuracy strategy switching. *Hum Brain Mapp.* 2012;33(7):1677-1688.

113. Geng J, Schnur TT, Janssen N. Relative speed of processing affects interference in Stroop and picture–word interference paradigms: evidence from the distractor frequency effect. *Lang Cog Neurosci.* 2014;29(9):1100-1114.

114. Drew MA, Starkey NJ, Isler RB. Examining the Link between Information Processing Speed and Executive Functioning in Multiple Sclerosis. *Arch Clin Neuropsychol.* 2009;24(1):47-58.

115. Eckert M, Keren N, Roberts D, Calhoun V, Harris K. Age-related changes in processing speed: unique contributions of cerebellar and prefrontal cortex. *Front Human Neurosci.* 2010;4(10).

116. Lee S-T, Park C-K, Kim JW, et al. Early cognitive function tests predict early progression in glioblastoma. *Neurooncol Pract.* 2015;2(3):137-143.

PART II

CHAPTER 2

Cognitive functioning in patients with nonfunctioning pituitary adenoma before and after endoscopic endonasal transsphenoidal surgery

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ABSTRACT

Purpose Patients with nonfunctioning pituitary adenomas (NFPAs) can suffer from cognitive dysfunction. However, the literature on longitudinal cognitive follow-up of patients undergoing endoscopic endonasal transsphenoidal surgery (EETS) is limited. This study was performed to investigate perioperative cognitive status and course in patients with NFPAs.

Methods Patients underwent computerized neuropsychological assessment 1 day before (n = 45) and 3 months after (n = 36) EETS. Performance in 7 domains was measured with a computerized test battery (CNS Vital Signs) and standardized using data from a healthy control group. We conducted analyses of cognitive performance at both time points and changes pre- to post-ETSS on a group and an individual level. Linear multiple regression analyses were employed to investigate predictors of cognitive performance.

Results On average, patients scored significantly lower in 6 of 7 cognitive domains before and after surgery than controls. Impairment proportions were significantly higher among patients (56% before surgery, 63% after surgery) than among controls. Patients showed no change over time in group-level (mean) performance, but 28% of individual patients exhibited cognitive improvement and 28% exhibited cognitive decline after surgery. Hormonal deficiency showed a positive correlation with verbal memory before surgery. Postoperative performances in all cognitive domains were predicted by preoperative performances.

Conclusion Cognitive impairment was present before and after EETS in over half of NFPA patients. Individual patients showed diverse postoperative cognitive courses. Monitoring of cognitive functioning in clinical trajectories and further identification of disease-related and psychological predictors of cognition are warranted.

INTRODUCTION

An increasing body of evidence indicates that patients with pituitary adenoma may suffer from cognitive dysfunction.[1,12,28,39] While executive functioning may show improvement before other domains, such as episodic memory or perceptual speed,[15,31] deficits do not necessarily resolve after successful medical treatment.[14,24,26,29]The degree of cognitive dysfunction has been linked tentatively to factors such as age[25] and the presence of an extrasellar component.[31] Although functioning adenomas that cause hormonal hypersecretion appear to be related to more dysfunction than nonfunctioning pituitary adenomas (NFPAs),[31,38,41] studies consistently show that patients with NFPA perform worse than healthy individuals.[4,6,38]

The available literature focusing on or including NFPAs largely comprises cross-sectional measurements of cognitive performance in patients who underwent varying surgical and nonsurgical treatments.[4–6,19,26,28,29,38]Prospective studies on perioperative cognitive functioning are scarce, but those that exist generally reported on short-term postsurgical improvement on a group level despite varying measurement methods.[15,31,41] A need remains for studies adopting standardized, validated measurements of cognitive function before and after surgical intervention. Moreover, group-level analyses can leave individual variations unnoticed, thereby possibly affecting the applicability of conclusions to clinical practice where patients with different characteristics are treated.

Cognitive dysfunction may pose an impediment to recovering regular functioning as it is related to mood disturbance,[37] work performance,[27] and quality of life.[23] Adequate screening in a clinical setting can help identify disturbance(s) at an early stage and guide further monitoring or intervention. Computerized testing offers an opportunity to evaluate cognitive function in a standardized and less labor-intensive way than traditional paper-and-pencil testing. The method has been shown to be effective in detecting cognitive dysfunction across patient groups,[7,21,40] whereas the sensitivity of well-known screening tools, such as the Mini-Mental State Examination (MMSE), in the brain tumor population is challenged.[22]

To our knowledge, the current study is the first to perform computerized cognitive screening over time in prospectively recruited patients with NFPAs undergoing resection. We used data from a Dutch control group of healthy individuals as reference for the following purposes: 1) to compare patients' cognitive performance before and 3 months after endoscopic endonasal transsphenoidal surgery (EETS), and 2) to investigate change in performance, on both a group and an individual level. In addition, we considered the influence of tumor expansion and hormonal deficiency on preoperative cognitive performance and the influence of hormonal deficiency and preoperative cognitive performance on postoperative cognitive performance in exploratory analyses.

MATERIALS AND METHODS

Design

Patients with primary brain tumors underwent neuropsychological assessment 1 day before and 3 months after surgery as part of their clinical care between November 2010 and March 2018 in the Neurosurgery Department of Elisabeth-TweeSteden Hospital. Data were used for research purposes after written consent was given by the patients. The study was approved by the Medical Ethics Committee of the hospital.

Participants

Prospective cognitive test data from patients with histologically proven NFPAs who underwent first-time EETS were collected for this study. Exclusion criteria were age under 18 years, a recent history of psychiatric or (progressive) neurological disorder (≤ 2 years), a history of intracranial neurosurgery, and characteristics that interfere with testing (e.g., severe visual deficits that prevent one from taking a computerized test).

Assessment Procedure

Assessments took place on the day of hospitalization (1 day before surgery) and when patients returned to the outpatient clinic for postoperative MRI evaluation (3 months after surgery). Assessments required approximately 60 minutes and included computerized evaluation of cognitive function, as well as completion of the Dutch version of the Hospital Anxiety and Depression Scale (HADS).[36] Sociodemographic variables were obtained via structured interview at the first assessment. Clinical data (symptoms at the time of presentation, reason for surgical intervention, and postsurgical events) were retrieved from medical records.

Measures

Cognitive functioning

Cognitive performance was assessed using CNS Vital Signs, a computerized neuropsychological test battery that is largely based on widely used tests, including the Symbol Digit Modalities Test and Stroop test.[13] The CNS Vital Signs tests used in this study took about 30–40 minutes and covered the following 7 domains: Verbal Memory, Visual Memory, Psychomotor Speed, Processing Speed, Reaction Time, Cognitive Flexibility, and Complex Attention.

Data on repeated CNS Vital Signs performance from 158 healthy Dutch individuals were previously collected by Rijnen et al.[33] and used to standardize patients' scores at each time point on each domain to z-scores, taking into account the effects of age, education, and sex that were demonstrated to influence CNS Vital Signs performance. Follow-up z-scores were also corrected for practice effects in repeated testing.

Radiological Tumor Characteristics

The Hardy-Wilson classification[42] was used to categorize the degree of preoperative extrasellar expansion (stages A–E) and invasion (grades I–IV). Signs of cavernous sinus invasion were classified according to Knosp grade (scores 0–4).[18] Evaluations were based on coronal section of T1-weighted gadolinium-enhanced 1.5-T MR images. For exploratory prediction analyses, we dichotomized the Hardy-Wilson classification for suprasellar growth, indicating the presence of extension beyond the optic chiasm (stage CD) or its absence.

Hormonal Status

Hormonal assessment was performed as part of perioperative endocrinological care before, 1 week after, and 2 weeks after surgery. Measurements included serum levels of thyroid-stimulating hormone, free thyroxine, adrenocorticotrophic hormone, cortisol, insulin-like growth factor 1, follicle-stimulating hormone, luteinizing hormone, prolactin, and testosterone or estradiol. From these measurements, functioning of the hormonal axes was established (normal function or hypofunction). For exploratory prediction analyses, we specifically used the status of the pituitary-adrenal (cortisol) and -thyroid axes (deficiency vs no deficiency), because of their established relationship with cognitive functioning.[2,10] Occurrences of transient and persistent central diabetes insipidus were obtained from the medical records.

Statistical Analysis

Group-Level Analyses: Cognitive Performance and Change

We conducted z-tests to compare the mean standardized z-scores for each of the 7 cognitive domains of patients to the norms (mean z-score = 0, SD = 1), for both the pre- and postoperative time points. The mean z-score of the patient group in each cognitive domain reflects the standardized difference (in SDs) between the patient and control sample and can be considered as Glass' delta effect size: $(M_{patients} - M_{controls})/SD_{controls}$. Change on group level was investigated using paired sample t-tests, for which Cohen's d effect sizes were calculated: $M_{difference}/SD_{difference}$.

Individual-Level Analyses: Cognitive Performance and Change

We inspected patients' individual performances in each domain for both time points. Individual z-scores of ≤ −1.5 (1.5 SDs below the mean; 6.7th percentile) were considered impaired. z-scores between −1.49 and −1.00 (6.8th–15.9th percentile) were considered low performances. We counted impaired and low performances per domain. Proportions at each time point were compared for patients versus healthy controls with chi-square tests and were compared over time within patients using McNemar's test. Standardized regression-based reliable change indices (RCIs)[20,34] were calculated to investigate reliable change over time in individual patients, accounting for confounding effects related to repeated test administration, including flawed test-retest reliability and practice effects. RCI values ≥ 1.645 or ≤ −1.645 (two-tailed 90% CIs) were considered reliable improvement or decline, respectively. Descriptive characteristics were computed for improvers, stable performers, and decliners. No statistical comparisons of these groups were performed, as achieved statistical power with the current group sizes would not be sufficient ($[1 - \beta] < 0.8$).

Prediction of Cognitive Performance

Power calculation with G*Power 3.1 (based on proposed small to medium effect sizes and $[1 - \beta] = 0.8$) indicated that a multiple regression analysis allowed for 2 predictors in this sample. We selected predictors based on reporting of particular importance to the NFPA population[2,10,31] and primary brain tumor patients undergoing resection.[32] Therefore, the relationships of preoperative performance (z-score) in each cognitive domain with suprasellar expansion and hormonal deficiency (dichotomized variables) and the relationships of postoperative performance with preoperative performance and postoperative hormonal status were investigated. Normal hormonal status and the absence of suprasellar growth were reference categories. Reflect-and-logarithmic transformation was performed for domains with nonnormal distribution of residuals.

All analyses were carried out using SPSS Statistics 22 (IBM Corp.). Adjusted levels of significance (α) using the procedure by Benjamini and Hochberg[3] were computed in the primary analyses to control for erroneous rejection of the null hypotheses in multiple testing (false discovery rate). Significance levels of 0.05 were adopted in the exploratory prediction analyses.

RESULTS

Patient Sample

Data from 45 patients (Table 1) who underwent preoperative assessment were included. Patients' mean age at the time of surgery was 59.7 years, in a predominantly male sample (67%). The distribution of patients according to Hardy-Wilson and Knosp classifications was available for 42 patients and is displayed in Table 2.

Transient or progressive visual deficits (e.g., hemianopia and diplopia) were the most common primary presenting symptom (31 patients, 69%), followed by headache (4 patients, 9%). Eight patients (18%) presented with other symptoms, including fatigue, anomia, malaise, and isolated epileptic insult. In 2 patients, the tumor was discovered during neuroimaging for a suspected unrelated illness (e.g., suspected transient ischemic attack). Tumor characteristics on MRI—compression of the optic chiasm, signs of tumor growth, pituitary (stalk) displacement—were the primary reason for surgical intervention (44 patients, 98%). Surgical intervention was indicated because of symptom worsening in between radiological evaluations in 1 patient (2%).

Nine patients (20%) did not complete the postoperative cognitive assessment (5 canceled the assessment; 1 patient was deceased; and 3 had logistical problems). We found no significant differences between patients who completed both cognitive assessments and those who underwent the preoperative assessment only, in terms of sociodemographic or clinical variables of interest and preoperative cognitive performances (all $p > 0.05$; data not shown).

Table 1. Patient characteristics

	Pre-op (n = 45)	**Post-op (n = 36)**
Male (%)	30 (67%)	26 (72%)
Age at time of surgery, yrs		
Mean, range	59.73 ± 12.07, 38–84	60.06 ± 12.17, 38–84
Educational level		
Low	16 (36%)	12 (33%)
Middle	12 (27%)	11 (31%)
High	17 (38%)	13 (36%)
HADS Anxiety score	6.85 ± 3.90	4.07 ± 3.49*
HADS Depression score	4.44 ± 3.84	3.93 ± 4.67
Postop events/complications		
CSF rhinorrhea	n/a	4 (9%)
Meningitis secondary to CSF rhinorrhea	n/a	2 (6%)
Nasal hemorrhage	n/a	1 (2%)
Central diabetes insipidus†		
Transient	0 (0%)	8 (22%)
Persistent	0 (0%)	3 (8%)
Anterior pituitary function		
Hypocortisolism no. (%, substituted no.‡)	15 (33%, 15)	13 (36%, 13)
Hypothyroidism no. (%, substituted no.‡)	18 (40%, 18)	20 (56%, 20)
Hypogonadism no. (%, substituted no.‡)	35 (78%, 5)	29 (81%, 7)
Growth hormone deficiency no. (%, substituted no.‡)	16 (36%, 1)	9 (25%, 2)

Values are presented as the number (%) of patients or as the mean ± SD.
*Significant change from pre- to postoperative measurement on a group level ($p < 0.01$).
†Transient: normalization at time of discharge. Persistent: continued therapy with desmopressin.
‡The number of patients receiving hormonal substitution therapy at pre- and postoperative measurements.

Table 2. Radiological classifications of NFPAs according to Hardy-Wilson and Knosp grades

Suprasellar Extension (H-W grade)		Parasellar Invasion (H-W grade)		Cavernous Sinus Invasion (Knosp grade)	
Category	*No.*	*Category*	*No.*	*Category*	*No.*
A (suprasellar cistern)	5	I (normal sella)	0	0 (no extension)	0
B (anterior recess of 3rd ventricle)	13	II (enlarged sella)	17	1 (no extension beyond intercarotid line)	13
C (displacement of 3rd ventricle floor)	15	III (localized floor perforation)	21	2 (no extension beyond lateral ICA tangent)	14
D (intradural)	1	IV (diffuse floor perforation)	4	3 (extension beyond lateral ICA tangent)	8
E (extradural)	8	V (distant spread)	0	4 (encasement of intracavernous ICA)	7

H-W = Hardy-Wilson; ICA = internal carotid artery

Group-Level Analyses: Cognitive Performance and Change

Before and after surgery, the patient sample showed significantly lower mean performance scores (false discovery rate–adjusted α-level 0.043) than the individuals from the normative sample in all domains (all $p \leq 0.02$) except Visual Memory ($p = 0.61$), with medium to large effect size (Table 3). Before surgery, Psychomotor Speed showed the lowest mean z-score, and thus greatest effect size (−0.90), followed by Reaction Time (−0.82). Similar effect sizes were found at 3-month postoperative assessment, where Reaction Time (−0.88) and Psychomotor Speed (−0.80) still showed the highest effect size. Paired sample t-tests showed no significant change in mean cognitive domain scores over time (all $p > 0.05$).

Individual-Level Analyses: Cognitive Performance and Change

Prior to surgery, 25 (56%) of 45 patients showed impairment in at least 1 cognitive domain, and 14 patients (31%) showed impairment in at least 2 domains. Four patients showed broad impairment (6 domains). The proportion of impairment among patients was significantly higher than in the control group (29% in 1 domain and 14% in 2 domains; $p = 0.02$). The highest proportions of impaired scores were observed for Psychomotor Speed (11 patients, 24%) (Table 4), followed by Complex Attention and Cognitive Flexibility (each 10 patients, 22%). These were significantly higher than those seen in the healthy control individuals (7%, 9%, and 9%, respectively; all $p < 0.05$). The postoperative proportion of impairment among patients (23 patients [64%]

in at least 1 domain; 11 patients [31%] in at least 2 domains) was not significantly different from that of the preoperative proportion ($p > 0.05$), but it was higher than that seen in the control sample at their second assessment ($p = 0.02$). Reaction Time and Verbal Memory showed the highest proportions of impairment after surgery (both 10 patients, 29%), again significantly higher than that seen in the control sample (7% and 5%; both $p < 0.05$), followed by Complex Attention (8 patients, or 23% vs 11% in controls; $p = 0.056$).

Thirteen (36%) of the 36 patients who underwent both pre- and postoperative assessments showed no reliable change in any of the domains. Ten patients (28%) showed decline (RCI ≤ −1.645) in one or more domains in the absence of improvement, and 10 patients (28%) showed improvement (RCI ≥ 1.645) in the absence of decline. Improvement and decline occurred concurrently in 3 patients (1 vs 2 domains, respectively, in 2 patients; and 1 vs 5 domains, respectively, in 1 patient). As shown in Table 4, we observed individual improvement most often for Reaction Time (7 patients, 20%), while none of the patients improved in the Visual Memory domain. Reliable decline was also most frequently observed in the Reaction Time domain (6 patients, 17%), followed by Cognitive Flexibility and Visual Memory (both 4 patients, 11%).

Group characteristics of patients whose cognitive performance improved, declined, and remained stable are presented in Table 5 (no statistical comparisons). All groups showed a decrease of > 2.5 points on the Anxiety subscale of the HADS from pre- to postoperative measurement. A decrease in the mean score on the Depression subscale of the HADS appeared to be greater among patients with improved cognitive performance (1.78 points) than among those with declined or stable cognitive performance (0.75 and 0.42 points, respectively). Seventy percent of those with a declined cognitive performance suffered from postsurgical hypothyroidism, compared to 40% in the other groups.

Table 3. Group-level standardized scores in cognitive domains before and 3 months after surgery

	Pre-op (n = 45)			Post-op (n = 36)			Mean Difference		
Domain	Mean Z	z-Test	*p*	Mean Z	z-Test	*p*	T0 –T3	*p*	Cohen's d
Verbal Memory	−0.34 ± 1.43	−2.31	0.02†	−0.57 ± 1.51	−3.30	<0.001	0.24 ± 1.32	0.31	0.18
Visual Memory	−0.08 ± 1.47	−0.51	0.61	−0.03 ± 1.13	−0.17	0.86	−0.05 ± 1.24	0.82	−0.04
Processing Speed	−0.59 ± 1.06	−3.93	<0.001†	−0.52 ± 0.90	−3.51	<0.001	−0.13 ± 0.72	0.29	−0.18
Psychomotor Speed	−0.90 ± 1.15	−5.99	<0.001†	−0.80 ± 0.93	−4.74	<0.001	−0.04 ± 0.81	0.75	−0.05
Reaction Time	−0.82 ± 1.69	−5.41	<0.001†	−0.88 ±−1.99	−5.23	<0.001	0.14 ± 1.46	0.56	0.10
Complex Attention	−0.64 ± 1.55	−4.18	<0.001†	−0.57 ± 1.58	−3.77	<0.001	−0.04 ± 1.62	0.84	−0.02
Cognitive Flexibility	−0.70 ± 1.45	−4.60	<0.001†	−0.54 ± 1.14	−4.15	<0.001	−0.13 ± 1.22	0.53	−0.11

Mean scores are presented ± SD.
Effect size: ≤ 0.50 = small; 0.51–0.79 = medium, ≥ 0.80 = large, .

Table 4. Cognitive status and change on individual level

	Pre-op cognition (n = 45)		Post-op cognition (n = 36)			
Domain	Impaired*	Low†	Impaired*	Low†	Improvement‡	Decline‡
Verbal Memory	9 (20%)§	1 (2%)	10/34 (29%)§	1 (3%)	4 (12%)	1 (3%)
Visual Memory	7 (16%)	4 (9%)	3/36 (8%)	1 (3%)	0 (0%)	4 (11%)
Processing Speed	9 (20%)§	7 (16%)	5/35 (14%)§	6 (17%)	4 (11%)	1 (3%)
Psychomotor Speed	11 (24%)§	9 (21%)§	7/35 (20%)§	6 (17%)§	2 (6%)	2 (6%)
Reaction Time	8 (18%)	5 (11%)	10/35 (29%)§	1 (3%)	7 (20%)§	6 (17%)
Complex Attention	10 (22%)§	5 (11%)	8/35 (23%)	2 (6%)	2 (6%)	3 (9%)
Cognitive Flexibility	10 (22%)§	9 (20%)	6/35 (17%)	5 (14%)§	5 (14%)	4 (11%)

Values are presented as the number (%) of patients.
*z-score ≤ −1.5, †−1.49 ≤ Z ≤ −1.,
‡RCI ≥ 1.645 = reliable improvement; RCI ≤ −1.645 = reliable decline.
§Proportion is significantly higher than in healthy control sample (p < 0.05).

Table 5. Preoperative and postoperative characteristics of patients organized by cognitive change

	Preop Characteristics			Postop Characteristics		
Characteristic	Improved (n = 10)	Declined (n = 10)	Stable (n = 13)	Improved (n = 10)	Declined (n = 10)	Stable (n = 13)
Male	8 (80.0%)	7 (70.0%)	9 (69%)			
Age at time of surgery ±SD	61.8 ± 10.8	62.7 ± 14.4	57.6 ± 12.7			
Educational level						
Low	1 (10%)	3 (30%)	7 (54%)			
Middle	6 (60%)	2 (20%)	3 (23%)			
High	3 (30%)	5 (50%)	3 (23%)			
HADS Anxiety score	6.14 ± 3.38	6.13 ± 2.53	6.69 ± 4.63	3.22 ± 2.54	3.63 ± 3.02	3.25 ± 2.56
HADS Depression score	4.00 ± 3.46	5.00 ± 4.11	4.00 ± 3.70	2.22 ± 2.05	4.25 ± 5.52	3.58 ± 4.08
Expansion above the optic chiasm	5 (50%)	5 (50%)	4 (31%)			
Secondary meningitis	NA	NA	NA	0 (0%)	2 (20%)	0 (0%)
Anterior pituitary function						
Hypocortisolism	3 (30%)	3 (30%)	2 (15%)	4 (40%)	4 (40%)	4 (31%)
Hypothyroidism	3 (30%)	4 (40%)	2 (15%)	4 (40%)	7 (70%)	4 (31%)
Hypogonadism	9 (90%)	8 (80%)	6 (46%)	8 (80%)	8 (80%)	6 (46%)
Growth hormone deficiency	6 (60%)	3 (30%)	1 (8%)	1 (10%)	2 (20%)	2 (15%)
Impairment ≥1 cognitive domain	6 (60%)	4 (40%)	8 (62%)	4 (40%)	6 (60%)	9 (69%)

NA = not applicable.
Values are presented as the number (%) of patients or as the mean ± SD. Percentages are calculated within each group (improvers, decliners, stable performers).

Prediction of Pre- and Postoperative Cognitive Performance

Preoperative performances in the domains were not predicted by the regression models that contained both variables of interest—hormonal deficiency and suprasellar extension (model p values > 0.05). Hormonal deficiency was, however, an independent positive predictor in the model for Verbal Memory ($\beta = 0.36$, $p = 0.02$), whereas suprasellar extension was not ($p > 0.05$).

Postoperative cognitive performances in all domains (Verbal Memory: $p < 0.01$, $F(2) = 8.95$, adjusted R^2 [adjR^2] = 0.33; Visual Memory: $p< 0.01$, $F(2) = 8.36$, adjR^2 = 0.26; Processing Speed: $p< 0.01$, $F(2) = 17.24$, adjR^2 =0.53; Psychomotor Speed: $p< 0.01$, $F(2) = 8.82$, adjR^2 = 0.32; Reaction Time: $p< 0.01$, $F(2) = 10.02$, adjR^2 = 0.47; Complex Attention: $p< 0.01$, $F(2) = 5.46$, adjR^2 = 0.16; and Cognitive Flexibility: $p= 0.01$, $F(2) = 5.3$, adjR^2 = 0.22) were significantly predicted by the regression models. Preoperative performance was the only significant predictor (all *p*'s< 0.02) for each postoperative performance, with standardized predictor coefficients ranging from $\beta = 0.43$ for Complex Attention up to $\beta = 0.76$ for Processing Speed. Postoperative hormonal deficiency was not an independent predictor (all *p*'s> 0.05) for postoperative performances.

DISCUSSION

This study prospectively evaluated cognitive performance and change over time with brief computerized testing of 45 patients with NFPA before and 3 months after EETS.

Our results support existing evidence of cognitive dysfunction in NFPA patients before[15] and after[4,25] treatment. As a group, patients showed significantly lower mean performance (status) scores than healthy controls in 6 of 7 domains, with moderate to large effect sizes, at both time points. Over half of patients showed impairment in at least 1 domain (56% before surgery, 63% after surgery). These rates of impairment among patients were significantly higher than those among controls.

Cognitive deficits in patients with NFPA may involve a broad range of domains instead of primarily concerning Verbal Memory, as previously proposed.[1] In accordance with Tiemensma et al.,[38] we found no difference between patients in our sample and the healthy controls on Visual Memory. This may reflect material-specific dysfunction (e.g., through left medial temporal structures),[17] rather than a general disturbance of memory-serving processes, such as sustained neuronal activation.[9,30] We must note that CNS Vital Signs memory domains, both visual and verbal, tap into immediate and delayed recognition instead of free recall, thereby not providing a full-scope measurement of memory.

The lack of group-level change in any of the domains in this study stands in contrast to available prospective findings in similar patient samples. Hendrix et al.[15] found performance normalization on measures of psychomotor and processing speed (Digit Symbol Substitution Test and Trail Making Test part A) 2 months after surgery, although their sample was small (n = 10). Wang et al.[41] reported improvement in multiple CAMCOG (Cambridge Cognitive Examination) subdomains at a 3-month postsurgical follow-up. The CAMCOG instrument is designed to distinguish mild dementia from normal cognitive aging,[35] with items that are less difficult than those on neuropsychological tests.[43] This can engender a low threshold to detect improvement and reduce suitability in the NFPA population.

We found markedly different individual courses, with almost equal proportions of patients showing no reliable change, improvement only, and decline only in cognition (36%, 28%, and 28%, respectively) and a small portion showing both improvement and decline (8%) that did not surface in the group-level results, which suggested a stable performance over time. Clinicians should be cautious when applying and communicating group-level information about postsurgical change to individual patients. Moreover, they should consider that different cognitive domains may show different rates of individual change.

Exploratory regression analyses of preoperative cognitive status showed that preoperative hormonal hypofunction (pituitary-adrenal axis; cortisol and/or pituitary-thyroid axis; and free thyroxine) was a positive predictor of verbal memory performance. The modulatory influence of circulating cortisol and thyroid hormone supposedly follows an inverted U shape, where suboptimal receptor occupancy, not just clinical deficiency, has been associated with memory dysfunction.[2,8,10] It may be that patients with pre-surgical clinical deficiency benefitted from replacement therapy (all patients with clinical deficiency in our sample received treatment), resulting in better performance than in patients with nonclinical suboptimal serum levels who were not receiving pharmacological treatment. We found no support for a significant influence of tumor expansion beyond the optic chiasm for cognitive performance, despite research suggesting that suprasellar growth can affect cognitive function,[31] possibly through disruption of adjacent (diencephalic) pathways. We acknowledge that categorization of suprasellar growth, as used in this study, although more easily determined in a clinical setting, provides a less precise measurement than a volumetric report.

Postoperative cognitive performances were not associated with postoperative hormonal status but were consistently predicted by the preoperative performances with notable effect sizes. Assessment of "cognitive fitness" as part of the clinical trajectory before surgery could be used to inform patients and target specific domains for further monitoring after resection.

Due to the sample size, we were limited in the number of candidate predictors of cognitive status we could adopt into the regression analyses, and statistical power was deemed too low to perform comparative tests of characteristics of the groups of patients whose cognitive status improved, declined, and remained stable over time. We did not adopt anxiety and depression symptoms in the prediction analyses, but we acknowledge that they might have played a role in cognitive performance—e.g., through attenuation of attentional control.[11,16] Individual patients can entertain variable levels of anxiety and depression in the perioperative period, which may have accounted for individual variation in cognitive status but also change. Notably, the group of patients whose cognitive status improved in our study appeared to show greater reduction in depressive symptoms than those whose cognitive status declined and remained stable.

The current results were derived from patients undergoing EETS, but findings may be generalizable to NPFA patients undergoing resection via the transsphenoidal approach with the microscope. Direct generalization of the longitudinal results to patients treated using a transcranial (microscopic) method is not warranted. In light of previous and current findings, we strongly recommend larger studies be performed to predict cognitive status and individual change therein, taking into account preoperative cognitive performance, as well as sociodemographic, disease-related (growth characteristics, tumor size, hormonal status, postsurgical events), and psychological (anxiety, depression) factors.

CONCLUSION

Computerized neuropsychological assessment showed lower cognitive performance in nearly all tested domains in patients with NFPA compared to healthy individuals before and 3 months after EETS. Impaired performance was found in more than half of the patients at both time points. Notably, nearly equal proportions of individual cognitive improvement, decline, and stable performance over time were found. Substantial individual variation in patterns of cognitive change after EETS thus seems present. This study emphasizes the need for the following: 1) cognitive evaluation of NFPA patients undergoing EETS to capture early impairment and/or subsequent decline and 2) caution in applying group-level results to individual patients, until multifaceted predictors of individual perioperative cognition are further established.

REFERENCES

1. Alsumali A, Cote DJ, Regestein QR, Crocker E, Alzarea A, Zaidi HA, et al: The impact of transsphenoidal surgery on neurocognitive function: A systematic review. *J Clin Neurosci.* 2017;42:1-6.
2. Bégin ME, Langlois MF, Lorrain D, Cunnane SC: Thyroid Function and Cognition during Aging. Curr *Gerontol Geriatr Res*. 2008:1-11.
3. Benjamini Y, Hochberg Y: Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J Roy Stat Soc B Met*. 1995;57:289-300.
4. Brummelman P, Elderson MF, Dullaart RP, van den Bergh AC, Timmer CA, van den Berg G, et al. Cognitive functioning in patients treated for nonfunctioning pituitary macroadenoma and the effects of pituitary radiotherapy. *Clin Endocrinol*. 2011;74:481-487.
5. Brummelman P, Sattler MG, Meiners LC, Elderson MF, Dullaart RP, van den Berg G, et al: Cognitive performance after postoperative pituitary radiotherapy: a dosimetric study of the hippocampus and the prefrontal cortex. *Eur J Endocrinol*. 2012;166:171-179.
6. Brummelman P, Sattler MGA, Meiners LC, van den Berg G, van der Klauw MM, Elderson MF, et al: Cognition and brain abnormalities on MRI in pituitary patients. *Eur J Radiol*. 2015;84:295-300.
7. Caine C, Deshmukh S, Gondi V, Mehta M, Tomé W, Corn BW, et al: CogState computerized memory tests in patients with brain metastases: secondary endpoint results of NRG Oncology RTOG 0933. *J Neurooncol.* 2016;126:327-336.
8. Wilson CB: *Neurosurgical management of large and invasive pituitary tumors* (ed): Clinical management of pituitary disorders. New York: Raven Press, 1979, pp335-342.
9. Correia N, Mullally S, Cooke G, Tun TK, Phelan N, Feeney J, et al: Evidence for a specific defect in hippocampal memory in overt and subclinical hypothyroidism. *J Clin Endocr Metab*. 2009;94:3789-3797.
10. Curtis CE, D'Esposito M: Persistent activity in the prefrontal cortex during working memory. *Trends Cogn Sci.* 2003;7:415-423.
11. de Kloet ER, Oitzl MS, Joëls M: Stress and cognition: are corticosteroids good or bad guys? *Trends Neurosci*. 22:422-426, 1999.
12. Derakshan N, Smyth S, Eysenck MW: Effects of state anxiety on performance using a task-switching paradigm: an investigation of attentional control theory. *Psychon B Rev*. 2009;16:1112-1117.
13. Grattan-Smith PJ, Morris JG, Shores EA, Batchelor J, Sparks RS: Neuropsychological abnormalities in patients with pituitary tumours. *Acta Neurol Scand*. 1992;86:626-631.
14. Gualtieri CT, Johnson LG: Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs. *Arch Clin Neuropsych*. 2006;21:623-643.
15. Guinan E, Lowy C, Stanhope N, Lewis P, Kopelman M: Cognitive effects of pituitary tumours and their treatments: two case studies and an investigation of 90 patients. *J Neurol Neurosur Psychiatry*. 1998;65:870-876.
16. Hendrix P, Griessenauer CJ, Hans E, Simgen A, Oertel J, Karbach J: Cognitive function surrounding resection of nonfunctioning pituitary adenomas with suprasellar extension: A prospective matched-control study. *J Clin Neurosci*. 2017;40:109-114.

17. Joormann J, Yoon KL, Zetsche U: Cognitive inhibition in depression. *Appl Prev Psychol.* 2007;12:128-39.

18. Kelley WM, Miezin FM, McDermott KB, Buckner RL, Raichle ME, Cohen NJ, et al: Hemispheric specialization in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. *Neuron*. 1998;20:927-936.

19. Knosp E, Steiner E, Kitz K, Matula C: Pituitary adenomas with invasion of the cavernous sinus space: a magnetic resonance imaging classification compared with surgical findings. *Neurosurgery*. 1993;33:610-617.

20. Lecumberri B, Estrada J, Garcia-Uria J, Millan I, Pallardo LF, Caballero L, et al: Neurocognitive long-term impact of two-field conventional radiotherapy in adult patients with operated pituitary adenomas. *Pituitary*. 2015;18:782-795.

21. Maassen GH, Bossema E, Brand N: Reliable change and practice effects: outcomes of various indices compared. *J Clin Exp Neuropsych.* 2009;31:339-352.

22. Meskal I, Gehring K, van der Linden SD, Rutten GJ, Sitskoorn MM: Cognitive improvement in meningioma patients after surgery: clinical relevance of computerized testing. *J Neurooncol*. 2015;121:617-625.

23. Meyers CA, Wefel JS: The use of the mini-mental state examination to assess cognitive functioning in cancer trials: no ifs, ands, buts, or sensitivity. *J Clin Oncol*. 2003;21:3557-3558.

24. Mitchell AJ, Kemp S, Benito-León J, Reuber M: The influence of cognitive impairment on health-related quality of life in neurological disease. *Acta Neuropsychiatr*. 2010;22:2-13.

25. Mussig K, Besemer B, Saur R, Klingberg S, Haring HU, Gallwitz B, et al: Deteriorated executive functions in patients with successful surgery for pituitary adenomas compared with other chronically ill patients. *J Int Neuropsych Soc*. 2011;17:369-375.

26. Mussig K, Leyhe T, Besemer B, Saur R, Haring HU, Gallwitz B, et al: Younger age is a good predictor of better executive function after surgery for pituitary adenoma in adults. *J Int Neuropsych Soc*. 2009;15:803-806.

27. Noad R, Narayanan KR, Howlett T, Lincoln NB, Page RC: Evaluation of the effect of radiotherapy for pituitary tumours on cognitive function and quality of life. *Clin Oncol.* 2004;16:233-237.

28. Nugent BD, Weimer J, Choi CJ, Bradley CJ, Bender CM, Ryan CM, et al: Work productivity and neuropsychological function in persons with skull base tumors. *Neurooncol Pract*. 2014;1:106-113.

29. Peace KA, Orme SM, Padayatty SJ, Godfrey HP, Belchetz PE: Cognitive dysfunction in patients with pituitary tumour who have been treated with transfrontal or transsphenoidal surgery or medication. *Clin Endocrinol*. 1998;49:391-396.

30. Peace KA, Orme SM, Thompson AR, Padayatty S, Ellis AW, Belchetz PE: Cognitive dysfunction in patients treated for pituitary tumours. *J Clin Exp Neuropsychol*. 1997;19:1-6.

31. Pereira AM, Tiemensma J, Romijn JA, Biermasz NR: Cognitive impairment and psychopathology in patients with pituitary diseases. *Neth J Med*. 2012;70:255-260.

32. Psaras T, Milian M, Hattermann V, Gerlach C, Honegger J: Executive functions recover earlier than episodic memory after microsurgical transsphenoidal resection of pituitary tumors in adult patients--a longitudinal study. *J Clin Neurosci*. 2011;18:1340-1345.

33. Rijnen SJM, van der Linden SD, Emons WHM, Sitskoorn MM, Gehring K: Test-retest reliability and practice effects of the computerized neuropsychological test battery CNS Vital Signs: A solution-oriented approach. *Psychol Assess*. 2018;12:1652-1662.

34. Rijnen SJM, Meskal I, Emons WHM, Campman CAM, van der Linden SD, Gehring K, et al: Evaluation of Normative Data of a Widely Used Computerized Neuropsychological Battery: Applicability and Effects of Sociodemographic Variables in a Dutch Sample. *Assessment*. 2017 (e-pub).

35. Rijnen SJM, Meskal I, Bakker M, De Baene W, Rutten GM, Gehring K, Sitskoorn MM: Cognitive outcomes in meningioma patients undergoing surgery: individual changes over time and predictors of late cognitive functioning. *Neuro Oncol*. 2019 (e-pub)

36. Roth M, Tym E, Mountjoy CQ, Huppert FA, Hendrie H, Verma S, et al: CAMDEX. A standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. *Brit J Psychiatry.* 1986;149:698-709.

37. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM: A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychol Med*. 1997;27:363-370.

38. Taphoorn MJB, Klein M. Cognitive deficits in adult patients with brain tumours: *Lancet Neurol*. 2004;3:159-168.

39. Tiemensma J, Kokshoorn NE, Biermasz NR, Keijser BJ, Wassenaar MJ, Middelkoop HA, et al: Subtle cognitive impairments in patients with long-term cure of Cushing's disease. *J Clin Endocr Metab*. 2010;95:2699-2714.

40. Tooze A, Gittoes NJ, Jones CA, Toogood AA. Neurocognitive consequences of surgery and radiotherapy for tumours of the pituitary: *Clin Endocrinol*. 2009;70:503-511.

41. van Loenen IS, Rijnen SJM, Bruijn J, Rutten GM, Gehring K, Sitskoorn MM: Group changes in cognitive performance after surgery mask changes in individual oatients with glioblastoma. *World Neurosurg*. 2018;117:e172-e9,.

42. Wang X, Tong X, Zou Y, Tian X, Mao Z, Sun Z: The impact on cognitive functions of patients with pituitary adenoma before and after surgery. *Neurol Sci.* 2017;38:1315-1321.

43. Wouters H, Appels B, van der Flier WM, van Campen J, Klein M, Zwinderman AH, et al: Improving the accuracy and precision of cognitive testing in mild dementia. *J Int Neuropsych Soc*. 2011;18:314-322.

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CHAPTER 3

The APOE ε4 allele in relation to pre- and postsurgical cognitive functioning of patients with primary brain tumors

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ABSTRACT

Background: Recent studies suggest a relationship between the APOE ε4 allele and cognitive outcome in patients treated for malignant brain tumors. Still, longitudinal investigations that include a pre-treatment cognitive assessment are lacking and APOE's effects in patients with benign tumors are understudied. This study investigated pre-surgical cognitive performance and post-surgical change in ε4 carrying and non-carrying patients with glioma and meningioma.

Methods: Neuropsychological test scores (CNS Vital Signs battery [7 measures], Digit Span Forward/Backward, Letter Fluency test) were obtained as part of a prospective study in which patients with meningioma and glioma underwent cognitive assessment one day before (T0, N=505), and three (T3, N=418) and twelve months after (T12, N=167) surgery. APOE isoforms were identified retrospectively. E4 carriers and non-carriers were compared with regard to pre-treatment cognitive performance on group and individual level. Changes in performances over time were compared with longitudinal mixed model analysis in the total sample and the subgroup receiving adjuvant treatment.

Results: Carriers and non-carriers did not differ with regard to pre-treatment performance. No significant main effect of ε4 carrier status or interaction between time (T0 to T12) and carrier status was found on any of the tests in the whole sample nor in the sample receiving adjuvant treatment.

Conclusions: This study found no evidence of increased vulnerability for pre-treatment cognitive dysfunction or cognitive decline within one year after surgery in APOE ε4 carrying meningioma and glioma patients. Investigations that include larger samples at longer-term follow up are recommended to investigate potential late treatment effects.

INTRODUCTION

Patients with primary brain tumors are at risk for cognitive dysfunction both before and after treatment.[1-4] Sociodemographic, clinical and tumor specific factors have been related to the variation in the affected domains and/or the severity of dysfunction.[5-11] Research into possible germ line genetic determinants of cognition, such as APOE, in this patient population is relatively limited.

The major alleles of the APOE gene - ε2, ε3, ε4 - code for three variants of the glycoprotein apolipoprotein E (ApoE2/E3/E4), which is a key player in lipid metabolism regulation in the CNS,[12] and facilitator of neuronal repair and plasticity processes.[13,14] However, the three ApoE isoforms possess different structural and functional properties that determine their effects in case of injury through numerous cellular pathways.[14-16]

ApoE4 specifically shows negative effects compared to the other isoforms[14] as it facilitates maladaptive responses to CNS damage and less effectively promotes repair processes.[17,18] Cognitive outcome in clinical populations including Alzheimer's dementia,[19] ischemic stroke,[20,21] Parkinson's disease[22] and breast cancer [23,24] appear related to ApoE4. ApoE4's detrimental effects might influence consequences of brain tumor growth and damage as well. Similarly to after acute injury,[25,26] ApoE4 may facilitate an enhanced inflammatory response that results in aggravated disruption of blood-brain barrier integrity and increased edema. In addition, less efficient myelin formation[27] may result in lower white matter integrity.[28] Moreover, adverse effects more specific to anti-tumor treatment, such as oxidative stress and alterations in neurogenesis, may also be isoform-dependent.[17,29-34]

Correa and colleagues were the first to study the role of the APOE ε4 allele in cognition in patients treated for CNS tumors.[5] In later studies, they found that ε4 carriers showed poorer verbal learning and recall[35], and were more susceptible to decline of attention and working memory[36] as compared to non-carriers years after treatment. Currently, the absence of prospective longitudinal assessment of cognitive function in literature and lacking investigation in other common primary brain tumors, such as meningioma, limit our understanding of the role of APOE ε4 in the course of cognitive functioning in this population.

Prospective investigation of APOE ε4's effects on cognition may improve our ability to (preoperatively) identify patients with a higher risk for tumor- and treatment related dysfunction in clinical practice and inform them accordingly. Moreover, it could allow for more tailored planning of treatment to optimize the balance between maximal anti-tumor effect while limiting disruption of cognition, and thereby other relevant outcomes, such as quality of life.[37] In this study, we analyzed APOE genotypes in patients with glioma and meningioma who underwent neuropsychological assessment before and after surgical (and adjuvant) treatment in order to investigate differences between ε4 carriers and non-carriers with regard to 1) pre-treatment cognitive performance (status), and 2) cognitive functioning over time (change) up to 12 months after surgery.

METHODS

Design & Procedure

Patients with meningioma or glioma underwent surgical debulking between November 2010 and September 2017 at the Neurosurgery department of Elisabeth-TweeSteden hospital, Tilburg, The Netherlands. NPA was performed as standard clinical care one day before (T0) and three months after (T3) surgery. All patients signed for informed consent for the use of the T0 and T3 NPA data in research. For research purposes only, and with separate informed consent, patients underwent NPA 12 months after surgery (T12, from January 2014 onwards). NPA was administered by a neuropsychologist or neuropsychologist in training (MSc/graduate level).

Clinically obtained blood samples were analyzed retrospectively if patients had not formally objected to usage of samples for purposes other than clinical monitoring. Consent was recorded by the Clinical Pathology laboratory. The study was conducted according to the principles of the Declaration of Helsinki (Fortaleza rev. 2013), and in accordance with the Medical Research Involving Human Subjects Act (WMO). The study protocol was approved by the Medical Ethics Trial Committee Brabant (file NL41351.008.12).

Sample

Data was used from adult patients with a newly diagnosed diffuse glioma (WHO grade II-IV) or meningioma (grade I-II) who had completed at least T0 NPA. Further exclusion criteria were: previous intracranial surgery, a recent history (≤ 2 years) of severe psychiatric or neurologic disorder, other major medical illnesses in the last year (e.g., cancer), no basic proficiency in Dutch, and inability to undergo NPA (e.g., due to severe visual or motor problems). Patient data described in the current study are partly described previous studies.[10,38-40]

Measures

Sociodemographic data

Age, sex, level of education (low, middle, high) were obtained through standardized interview at T0.

Clinical data

Histopathological diagnosis, tumor location, use of corticosteroids, use of anti-epileptic drugs (AED), and adjuvant treatment were obtained from electronic medical records. Adjuvant treatment was dichotomized (chemo- and/or radiotherapy versus no adjuvant modality). Preoperative tumor volume was obtained through semi-automatic segmentation with either Brainlab Elements software or ITK-snap software, and expressed in cm^3.

Cognitive data

NPA comprised the formal Dutch translation of the CNS Vital Signs (CNS VS) computerized test battery, see Supplementary Table 1 for a description of the seven tests that were used: Verbal Memory test (VEM), Visual Memory test (VIM), Symbol Digit Coding test (SDC), Shifting Attention test (SAT), Continuous Performance test (CPT), Stroop test I and Stroop test III. The local software application of CNS VS was used on a notebook computer. Additionally, three paper-and-pencil tests were administered: a Letter fluency task[41], and, from 2015 onwards, a Digit Span Task (Forward and Backward).[42]

Standardization of test scores. Patients' raw scores on CNS VS were converted into Z-scores using data from 158 Dutch healthy controls, adjusting for demonstrated effects of age, sex, educational level, and, for T3 and T12 data, also for practice effects.[38] Digit Span scores were standardized in a comparable manner using data from a healthy control group obtained as part of an ongoing Clinical Trial (CAR study A, ClinicalTrials.gov reference nr. NCT02953756), and described by Verhaak and colleagues.[44] Fluency scores were standardized into Z-scores, using published norms.[41] These scores were standardized for educational level, but not sex or age, since these were not demonstrated to influence performance. Z-scores of each patient on each test were also dichotomized into impaired (Z-score ≤-1.5) or unimpaired.

APOE genotype

APOE isoforms were determined by the department of Laboratory Medicine using assay kits (ViennaLab, Diagnostics GmbH) involving a procedure of DNA isolation, polymerase chain reaction (PCR) amplification using biotinylated primers, and reverse-hybridization. Obtained genotypes were dichotomized into ε4 carrier (heterozygous or homozygous) vs. non-carrier (i.e., ε2 or ε3 carrier).

Psychological data

The Dutch translation of the Hospital Anxiety and Depression Scale (HADS[43]) was administered at each time-point (T0, T3, T12) to screen for symptoms of anxiety and depression.

Statistical analyses

Characteristics of APOE ε4 carriers and non-carriers

Potential baseline differences regarding sociodemographic (age, education level, sex), clinical (histopathology, frontal lobe involvement, tumor hemisphere, tumor volume, use of AED, use of corticosteroids and adjuvant treatment), and psychological (Anxiety and Depression) scores between ε4 carriers and non-carriers were investigated in the total sample, and stratified according to brain tumor diagnosis. Chi-square tests of independence were used for categorical variables, independent samples t-tests for continuous variables with normal distributions, and Mann-Whitney U tests for continuous variables with skewed distributions (α=.05).

Preoperative cognitive performance

Mean performance of the entire sample was compared to healthy controls using Z-tests. Subsequently, mean performances of carriers vs. non-carriers in the patient sample were compared for each test with independent samples t-tests and Mann-Whitney U tests. The proportions of impairment for carriers vs. non-carriers on each test were compared using Chi-square tests. In case of baseline differences on any of the sample characteristics previously described, that variable was adopted as a covariate in analysis of variance (ANCOVA) or as a layer in Chi-square tests. To inspect potential bias in the long-term follow up sample, we compared pre-operative performances (mean performances and impairment proportions) of patients who completed T12 assessment and those who dropped out before T12.

Cognitive functioning over time

We conducted Linear Mixed Model (LMM) analyses to investigate the course of cognitive performances over time (1 model per cognitive test), initially in the total patient sample. In the longitudinal LMM, Time (T0,T3,T12) was level 1 and its measurements were nested in the patients at level 2. Because only three time points were involved, we adopted a linear effect of Time for all models. Intercepts were specified as random effects, allowing for individual estimations of the data of each patient. Random slopes were added to those models if they significantly improved model fit (likelihood ratio test, α=.05). Among the tested correlation structures (autoregressive, continuous autoregressive, compound symmetry, general correlation matrix, scaled identity), the one providing the best fit based on the Akaike Information Criterion (AIC) for the majority of the models was adopted uniformly.

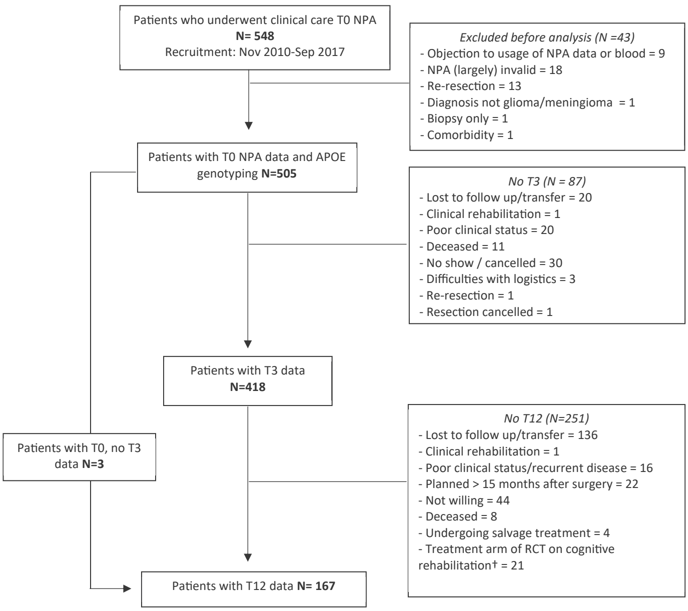
First, we created models with only Time as predictor to investigate the overall course of performances without any other predictors. In the final models, we included a Time*Carrier status interaction (non-carrier as reference group). We also included a Time*Diagnosis interaction to account for possible differences in performance over time between meningioma and glioma patients (glioma as reference group). Similar models were constructed to investigate the effect of carrier status for the T0-T3 interval and T3-T12 interval separately, using Time as factor instead of a continuous variable (no random slopes). Within the group of patients who received adjuvant treatment -regardless of diagnosis-, we performed ancillary analyses, again of Time*Carrier status.

We used the restricted maximum likelihood (REML) algorithm to estimate model parameters. Global fits of the models (models with only Time as predictor vs the final models) were compared using AIC, and tested with likelihood ratio tests in case of a significant effect of carrier status. Analyses of the data[45] were performed using SPSS software (version 24) and Rstudio software (lme4 and nlme packages[46,47]). We adopted a correction for multiple testing (taking into account the 10 tests we performed to investigate all cognitive measures) per main analysis (pre-treatment performance, post-treatment change with Time only, and post treatment change with APOE carrier status) using the False Discovery Rate correction procedure by Benjamini and Hochberg[48] (original α=.05).

RESULTS

Characteristics of APOE ε4 carriers and non-carriers

Figure 1 shows a flow chart of patient inclusion. Baseline characteristics of the sample are displayed in Table 1. There were no significant differences for any of the inspected sociodemographic, psychological or clinical variables between APOE ε4 carriers and non-carriers in the total sample (*p*'s >.05). In the meningioma group, there was a significantly larger proportion of frontal lobe tumors among non-carriers as compared to carriers, *p*=.03).



† NCT Number: NCT03373487

Figure 1. Flow chart of patient inclusion and attrition.

Table 1. Baseline characteristics of included patients (T0)

Characteristic	Glioma (N=263)		Meningioma (N=242)		Total (N=505)	
	ε4 carrier (n=64)	non-carrier (n=199)	ε4 carrier (n=64)	non-carrier (n=178)	ε4 carrier (n=128)	non-carrier (n=377)
Sociodemographic						
Age M±SD	53.2 ± 14.8	53.2 ± 13.8	55.9 ± 12.7	57.0 ± 11.6	54.9 ± 13.9	55.3 ± 13.1
Female, n (%)	28 (44)	71 (36)	41 (64)	135 (76)	69 (54)	206 (55)
Education, n(%)						
Low	20 (31)	57 (29)	25 (39)	63 (35)	45 (35)	120 (32)
Middle	19 (30)	69 (34)	14 (22)	57 (32)	40 (31)	126 (33)
High	25 (39)	73 (37)	25 (39)	58 (33)	43 (34)	131 (35)
Clinical						
Diagnosis, n(%)						
LGG WHO II	21 (30)	59 (30)	n/a	n/a	19 (15)	59 (16)
HGG WHO III/IV	45 (70)	140 (70)	n/a	n/a	45 (35)	140 (37)
MEN WHO I	n/a	n/a	61 (95)	166 (93)	64 (50)	178 (47)
MEN WHO II	n/a	n/a	3 (5)	12 (7)		
Frontal involvement	34 (53)	101 (51)	31 (48) †	114 (64) †	65 (51)	215 (57)
Lesion hemisphere						
Left	30 (47)	81 (40)	24 (38)	68 (38)	54 (42)	149 (40)
Right	33 (52)	117 (59)	36 (56)	87 (49)	69 (54)	204 (54)
Bilateral	1 (1)	1 (1)	4 (6)	23 (13)	5 (4)	24 (6)
Tumor volume (n=235) Med (range)	24.0 (15.3-80.1)	42.8 (2.0-139.1)	35.1 (30.4-128.2)	29.5 (4.5-150.2)	30.9 (3.4–128)	31.0 (4.5-150)
AED use, n(%)	32 (53)	83 (43)	58 (33)	42 (23)	47 (38)	125 (34)
Corticosteroid use, n(%)	29 (48)	107 (56)	21 (33)	15 (23)	50 (41)	165 (45)
Adjuvant treatment, n(%)	46 (72)	146 (73)	4 (6)	13 (7)	50 (39)	159 (42)
Rtx	46 (72)	146 (73)	4 (6)	13 (7)	50 (39)	159 (42)
Chtx‡	36 (56)	117 (59)	0 (0)	0 (0)	36 (29)	117 (31)
Concurrent Rtx/Chtx	36 (56)	117 (59)	0 (0)	0 (0)	36 (29)	117 (31)
Psychological						
HADS Anxiety M±SD	7.0 ± 4.5	6.9 ± 4.3	7.1 ± 4.3	7.1 ± 4.3	7.0 ± 4.4	7.0 ± 4.2
HADS Depression M±SD	5.3 ± 3.7	4.8 ± 3.4	5.8 ± 4.7	6.1± 4.9	5.6 ± 4.3	5.4 ± 4.2

Information was available for AED use at T0 n=124 (ε4 carriers) vs. 367 (non-carriers), Corticosteroid use at T0 n=128 vs. 367, Adjuvant Tx: n= 126 vs 372

† significant difference between carriers and non-carriers within the diagnostic group, *p*<.05.

‡ Temozolomide, Lomustine or PCV (Procarbazine-Lomustine-Vincristine)

Baseline cognitive performances in the total sample

Z-tests showed that our sample performed worse than healthy controls on all NPA measures (all *p*'s <.001, data not shown). As a group, patients who returned for T12 follow up showed better pre-surgical performances than those who did not return for T12 on all tests (*p*'s<.05, data not shown) except Finger Tapping, Continuous Performance, Fluency and Digit Span Forward and Backward. The baseline proportion of impaired performances was also lower among patients who returned for T12 follow up for Symbol Digit Coding, Shifting Attention, Stroop III and Fluency tests (*p*'s<.05, data not shown).

Baseline cognitive performances of ε4 carriers and non-carriers

No significant differences were found between carriers and non-carriers in mean performance on any of the tests under the adjusted α (BH-corrected α=.005), see Table 2. No significant differences were found between carriers and non-carriers with regard to the proportions of impaired performances (BH-corrected α=.005), see Figure 2.

Cognitive functioning over time of ε4-carriers and non-carriers

Table 2 and Figure 3 show group performances on each test for carriers and non-carriers over time. Table 3 shows results of the LMM. We found a positive effect of Time for scores on the Verbal Memory test, Symbol Digit Coding test, Shifting Attention test, Stroop test I and II, and Fluency test (BH-corrected adjusted α=.03, range β=.02 to β=.05, p's<.01). In the final models, we found no significant main effects of ε4 carrier status nor Time*ε4 carrier status interactions (BH-corrected α=.005). No significant effects were found for Time*Diagnosis, except for Fluency performance in the T0-T3 interval. Meningioma patients showed more improvement than glioma patients on this test (*p*=.001), see Table 3. Analyses in the group of patients who received adjuvant treatment (chemotherapy and/or radiotherapy) revealed no significant main effect of carrier status or Time*carrier status interaction (data not shown), *p*'s >.10.

Table 2. Mean Z-scores (status) for carriers and non-carriers at each measurement (T0, T3, T12) and baseline comparisons

	T	Carrier status	N	Verbal Memory † (VEM)	Visual Memory † (VIM)	Symbol Digit Coding† (SDC)	Shifting Attention † (SAT)	Continuous Performance† (CPT)	Stroop test part I† (Stroop I)	Stroop test part III† (Stroop III)	Verbal fluency (Fluency)	Digit Span FW (DSFW)	Digit Span BW (DSBW)
GLIO	**T0**	ε4 carrier	64	-0.70±1.37	-0.59±1.39	-0.97±1.27	-1.21±1.66	-0.79±1.58	-0.71±1.71	-1.40±2.51	-0.36±1.12	-0.40±0.91	-0.71±0.51
		non-carrier	199	-0.66±1.27	-0.59±1.37	-1.06±1.46	-0.87±1.62	-0.62±1.45	-1.05±1.97	-1.40±2.32	-0.86±1.12	-0.25±1.30	-0.45±1.14
		p		.80	.99	.68	.16	.42	.32	.73	.01	.91	.41
	T3	ε4 carrier	50	-0.91±1.46	-0.52±1.41	-0.99±1.08	-1.10±1.49	-1.14±1.93	-0.69±1.46	-1.25±1.86	-0.56±1.15	-0.73±0.97	-1.00±1.35
		non-carrier	149	-0.72±1.29	-0.58±1.23	-0.90±1.25	-0.94±1.60	-0.97±1.58	-1.02±1.85	-1.37±1.83	-0.71±1.17	-0.59±1.11	-0.71±1.45
	T12	ε4 carrier	12	-0.26±0.85	-0.77±0.78	-0.92±1.11	-0.36±1.06	-0.61±1.10	-0.82±1.27	-0.27±1.72	0.01±1.33	-0.83±0.98	-0.59±0.22
		non-carrier	51	-0.18±0.94	-0.41±1.17	-0.46±1.31	-0.42±1.20	-0.27±1.01	-0.65±1.38	-0.47±1.70	-0.44±1.16	-0.79±1.20	-0.63±1.27
MEN	**T0**	ε4 carrier	178	-0.93±1.47	-0.65±1.26	-0.92±1.36	-0.88±1.82	-0.16±1.28	-0.98±2.35	-0.40±2.41	-0.62±1.05	-0.41±1.19	-1.21±0.99
		non-carrier	64	-0.55±1.24	-0.46±1.18	-1.08±1.37	-0.75±1.50	-0.47±1.52	-0.76±1.96	-0.11±1.92	-0.81±1.05	-0.53±1.12	-0.71±0.92
		p		.05	.28	.45	.60	.15	.41	.36	.37	.71	.06
	T3	ε4 carrier	59	-1.07±1.32	-0.32±1.33	-0.70±1.18	-0.77±1.67	-0.56±1.24	-0.89±1.95	-1.00±1.78	-0.05±1.37	-0.66±1.32	-0.95±1.45
		non-carrier	160	-0.80±1.29	-0.34±1.24	-0.83±1.18	-0.69±1.39	-0.70±1.29	-0.62±1.69	-0.90±1.67	-0.42±1.10	-0.53±0.82	-0.41±1.15
	T12	ε4 carrier	29	-0.63±1.17	-20±1.17	-0.49±1.03	-0.23±1.17	-0.35±1.08	-0.52±1.76	-0.51±1.77	-0.27±0.95	-0.85±1.02	-0.83±1.37
		non-carrier	75	-0.35±1.06	-0.35±1.13	-0.48±0.86	-0.22±1.12	-0.35±1.10	0.00±1.07	-0.50±1.47	-0.07±1.08	-0.27±0.89	-0.38±0.92
Total	**T0**	ε4 carrier	128	-0.82±1.42	-0.62±1.28	-0.95±1.31	-1.04±1.74	-0.48±1.47	-0.85±2.06	-1.40±2.46	-0.52±1.09	-0.41±1.02	-0.92±1.32
		non-carrier	377	-0.61±1.26	-0.53±1.28	-1.07±1.42	-0.81±1.56	-0.55±1.48	-0.91±1.96	-1.26±2.14	-0.83±1.08	-0.38±1.22	-0.57±1.04
		p		.12	.48	.46	.31	.63	.56	.97	.02	.91	.10
	T3	ε4 carrier	109	-1.00±1.38	-0.42±1.37	-0.83±1.14	-0.91±1.59	-0.81±1.59	-0.81±1.75	-1.11±1.80	-0.27±1.30	-0.69±1.15	-0.97±1.38
		non-carrier	309	-0.76±1.29	-0.45±1.24	-0.86±1.21	-0.81±1.49	-0.83±1.43	-0.81±1.78	-1.10±1.76	-0.56±1.14	-0.56±0.96	-0.61±1.29
	T12	ε4 carrier	41	-0.39±1.16	-0.36±1.10	-0.61±1.05	-0.26±1.13	-0.43±1.08	-0.60±1.63	-0.44±1.73	-0.18±1.06	-0.85±0.96	-0.75±1.10
		non-carrier	126	-0.28±1.01	-0.37±1.15	-0.47±1.07	-0.30±1.15	-0.31±1.06	-0.27±1.25	-0.49±1.56	-0.22±1.12	-0.48±1.04	-0.48±1.06

† CNS Vital Signs computerized test battery

Values displayed are M ± SD. P values refer to group comparison at T0 (FDR adjusted α=.005).

Sample sizes for the Digit Span test T0= 42 vs 94, T3 n=36 vs 81, T12 n=12 vs 24, for the Fluency test T0 n=97 vs. 281, T3 n=87 vs 255, T12 n=30 vs 91.

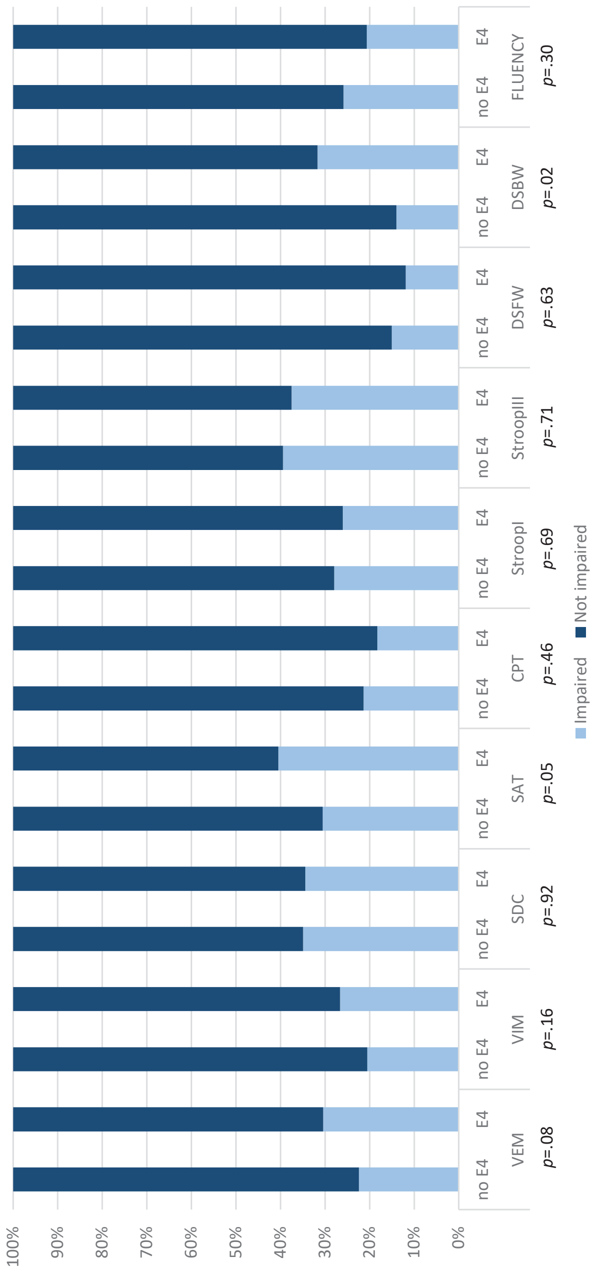


Figure 2. Proportions of cognitive impairment at baseline (T0). Bars represent proportions (%) of impaired (light) and non-impaired (dark) performances on each test. P-values refer to statistical testing of impairment proportions between the two groups

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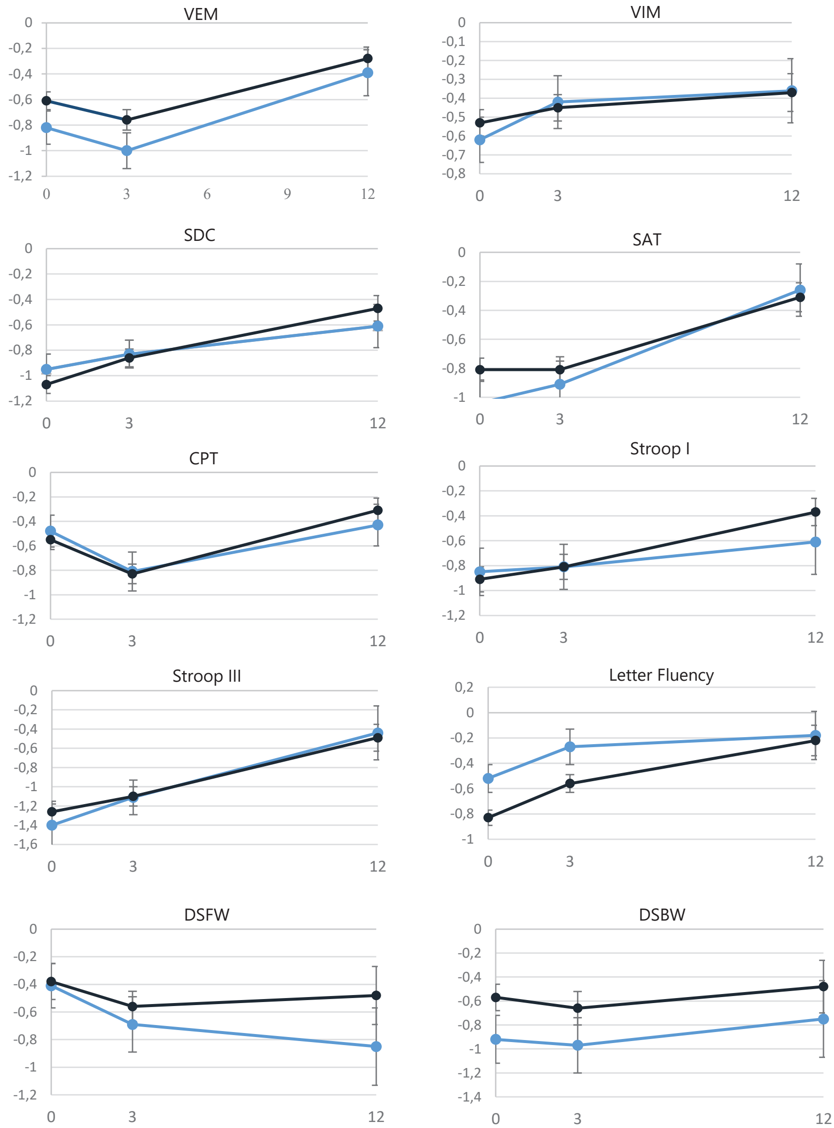

Figure 3. Mean performances ± SEM over time on each test stratified by ε4 carrier (light) vs. non carrier (dark) for the total sample.

Table 3. Results from the LMM analysis of (change in) cognitive performances over time (T0, T3, T12) in the total sample

		Verbal Memory†	Visual Memory	Symbol Digit Coding†	Shifting Attention†	Continuous Performance	Stroop test I†	Stroop test III†	Fluency	DSFW	DSBW
Time model	Model AIC	3290	3352	3156	3451	3470	4026	4012	2411	813	893
Time	b(SE)	0.02(0.01)	0.00(0.01)	0.03(0.01)	0.03(0.01)	0.01(0.01)	0.04(0.01)	0.05(0.01)	0.03(0.01)	-0.02(0.01)	0.01(0.01)
	p	.003	.563	<.001	<.01	.328	<.001	<.001	<.001	.132	.615
Final model	Model AIC	3308	3372	3173	3467	3484	4035	4026	2424	832	906
Time Diagnosis	b(SE)	-0.02(0.01)	0.01(0.02)	0.01(0.01)	0.02(0.02)	-0.02(0.02)	0.04(0.02)	-0.00(0.02)	0.02(0.01)	0.04(0.02)	0.07(0.03)
	p	.198	.678	.398	.241	.313	.108	.979	.207	.104	.022
Time Carrier	b(SE)	0.00(0.02)	.01(0.02)	-0.02(0.01)	0.00(0.02)	-0.03(0.02)	-0.05(0.03)	-0.01(0.02)	-0.02(0.02)	-0.03(0.02)	-0.00(0.03)
	p	.903	.779	.137	.904	.088	.073	.899	.123	.252	.962
Diagnosis	b(SE)	0.00(0.11)	0.16(0.10)	0.05(0.12)	0.15(0.14)	0.29(0.12)	0.13(0.17)	0.30(0.18)	0.02(0.11)	-0.13(0.17)	-0.15(0.19)
	p	.968	.119	0.698	.275	.020	.443	.110	.346	.457	.355
Carrier	b(SE)	-0.22(0.13)	-0.07(0.12)	0.13(0.13)	-0.21(0.16)	0.02(0.14)	0.08(0.19)	-0.16(0.21)	0.32(0.12)	-0.04(0.19)	-0.37(0.20)
	p	.092	.572	.335	.181	.881	.673	.452	.010	.810	.069
Final model: interval T0T3	Model AIC	3293	3364	3179	3476	3451	4042	4035	2404	824	879
T0T3 Diagnosis*	b(SE)	-0.25(0.18)	0.22(0.13)	0.15(0.10)	0.11(0.13)	0.03(0.12)	0.07(0.19)	0.34(0.16)	0.35(0.10)	0.16(0.18)	0.53(0.22)
	p	.167	.093	.126	.156	.826	.699	.038	.001	.383	.016
T0T3 Carrier*	b(SE)	-0.08(0.12)	0.13(0.15)	-0.06(0.11)	-0.00(0.15)	-0.12(0.14)	-0.09(0.22)	0.01(0.19)	0.03(0.12)	-0.07(0.19)	-0.01(0.23)

3

Table 3. Continued.

		Verbal Memory†	Visual Memory	Symbol Digit Coding†	Shifting Attention†	Continuous Performance	Stroop test I†	Stroop test III†	Fluency	DSFW	DSBW
	p	.523	.400	.608	.983	.379	.669	.966	.818	.731	.976
Diagnosis	b(SE)	0.03(0.12)	0.08(0.11)	-0.00(0.12)	0.14(0.14)	0.29(0.13)	0.14(0.17)	0.17(0.18)	-0.03(0.11)	-0.13(0.18)	-0.30(0.20)
	p	.802	.458	.996	.324	.028	.395	.345	.810	.479	.144
Carrier	b(SE)	-0.23(0.13)	-0.11(0.13)	0.13(0.13)	-0.31(0.16)	0.03(0.15)	0.07(0.20)	-0.16(0.21)	0.28(0.13)	-0.05(0.20)	-0.37(0.22)
	p	.0752	.407	.378	.183	.842	.736	.446	.029	.794	.091
Final model: interval T3T12	Model AIC	3293	3364	3179	3476	3451	4042	4035	2404	824	897
T3T12 Diagnosis*	b(SE)	-0.17(0.18)	-0.13(0.20)	0.03(0.15)	0.17(0.20)	-0.29(0.18)	0.33(0.28)	-0.26(0.240	-0.14(0.17)	0.26(0.28)	0.20(0.35)
	p	.349	.494	.817	.391	.109	.244	.286	.447	.363	.573
T3T12 Carrier*	b(SE)	-0.06(0.21)	-0.07(0.22)	-0.18(0.17)	-0.05(0.23)	-0.21(0.21)	-0.49(0.32)	-0.12(0.28)	-0.32(0.19)	-0.18(0.30)	0.00(0.36)
	p	.770	.760	.300	.838	.323	.130	.664	.086	.338	.993
Diagnosis	b(SE)	-0.05(0.13)	0.31(0.12)	0.15(0.12)	0.25(0.15)	0.31(0.14)	0.22(0.18)	0.51(0.19)	0.33(0.12)	0.03(0.19)	0.23(0.21)
	p	.692	.014	.219	.099	.024	.237	.341	.005	.897	.278
Carrier	b(SE)	-0.19(0.14)	0.02(0.14)	0.07(0.14)	-0.22(0.17)	-0.10(0.16)	-0.03(0.21)	-0.17(0.22)	0.31(0.12)	-0.11(0.21)	-0.38(0.23)
	p	.190	.888	0.619	.209	.546	.892	.449	.020	.572	.104

‡ε4 non-carrier [as reference category] vs ε4 carrier, § Glioma [as reference category] vs meningioma

† random slopes of Time

Autoregressive correlation matrix was adopted for the final models with Time as continuous predictor. In the interval analyses (Time as factor, T0-T3, T3-T12), scaled identity was specified (covariances set to 0).

Corrected α of final models: α=.005, corrected α of models with effect of Time only: α.03

DISCUSSION

The current prospective longitudinal study investigated whether patients with glioma or meningioma carrying the APOE ε4 allele showed greater vulnerability for cognitive dysfunction before treatment (1 day before surgery) and worse cognitive functioning over the course of treatment (3 and 12 months after surgery) as compared to non-carriers. We found no evidence for significantly worse pre-treatment cognitive performance, i.e., a lower group performance or higher prevalence of impairment, in ε4 carriers. Overall (without distinction based on APOE genotype), patients showed significant improvement from the pre-surgical to the 12 month postsurgical measurement on tests tapping into verbal memory (Verbal Memory test), psychomotor speed (Symbol Digit Coding test), and executive functioning (Shifting Attention test, Stroop test, and Verbal fluency). We found no significant differences in performance over time between carriers and non-carriers on any of the tests.

As previous investigation of APOE's effects in brain tumor patients did not include a pre-treatment measurement, it remained unknown to what extent worse cognition in carriers after treatment was actually related to preexisting dysfunction.[49] We expected a small negative effect in the ε4 allele carriers before start of treatment, based on ApoE4's modulation of cerebrovascular function[16,26] and white matter integrity[50] in response to injury. The lack of differences in pre-treatment performances between carriers and non-carriers may be related to the temporal pattern of brain tumor injury. Brain tumor growth involves diffuse infiltration and/or compression over a period of years, as opposed to acute damage. Especially in case of tumors with lower lesion momentum, APOE ε4 carriers may exert greater compensatory neural recruitment or "cognitive effort" that may be reflected in altered functional connectivity,[28] but not a poorer test performance. We also note that large standard deviations were present for most of the (computerized) test scores at baseline. Substantial within-group variation is not uncommon in brain tumor patients, but it could have complicated detection of potential small effect sizes from an allelic variation.

Based on longitudinal research in treated (non-)CNS cancer patients, we expected ε4 carriers to show worse performances over time (i.e., less recovery) compared to non-carriers on tests of executive functioning, (working) memory and processing speed.[24,35,36,51,52] A myriad of pathways,[48] including vascular abnormalities, sub-efficient myelin regulation, increased oxidative stress and treatment-related toxicity, [17,30,31,34] could contribute this difference in cognitive outcome. Our results did, however, not illustrate poorer trajectories of cognitive functioning in the total sample nor in the subgroup that received adjuvant treatment.

We note some methodological differences between studies that might account for the different findings. The longitudinal study by Correa and colleagues[36] that reported a ε4-related risk for decline in Digit Span performance, obtained cognitive measurements at later time-points (first assessment 4±3.4 years after completion of treatment and second assessment 5.2±0.8 years after that). Similarly, a study by Ahles and colleagues included long-term survivors of breast cancer 8.8±4.3 years post-treatment [23]. Our measurements were obtained up to 12 months post-surgery (about 9 months after completion of radiotherapy, and about 3 months after completion of chemotherapy, depending on clinical and tumor characteristics). A longitudinal study by Ahles and colleagues [51] investigating changes from pre up to 18 months post-chemotherapy in breast cancer patients also found no main effect of APOE. Late cognitive effects of treatment-induced processes that continue >6 months after radiation, such as capillary loss [53] and apoptosis [54], may be captured better at later follow ups than those in our study.

We applied correction for multiple testing, thereby holding a more stringent cut off for significant effects than other studies. Still, differences for baseline proportions of impairment Digit Span Backward and Shifting Attention tests were relatively large (>10% more impairment in carriers as compared to non-carriers) and could have been considered significant under an unadjusted significance level. In addition, mean performances for Letter Fluency appeared higher in carriers than non-carriers at baseline, but similar at 12 month follow up, which indicates more improvement in non-carriers. These tests measure different facets of executive function, and a significant difference for Digit Span Backward was also found in previous research [36]. Future investigations may therefore focus primarily on executive measures.

While our sample sizes at pre- and first post-surgical measurement were large, 41 ε4 carriers and 126 non-carriers remained for the relevant time-point 12 months post-surgery. This left us unable to include additional variables that might moderate the relationship between APOE and long-term cognition For example, preclinical research has shown that adverse cognitive effects of radiation in ε4 carriers may manifest particularly in females.[34] Our adjuvant treatment sample naturally comprised a large proportion of high-grade glioma that occur more commonly in males.[55] In addition, mixed results regarding the effect of APOE ε4 on cognition have been found for different age groups, i.e., a positive effect in middle-aged or younger adults versus a negative effect in older adults.[27,56] Our sample reflected the prevalence of brain tumors across age groups.

The degree to which APOE ε4 moderates cognition in patients with brain tumors remains somewhat inconclusive. While APOE ε4 might be related to a cognitive phenotype [27] conflicting results have also been reported in other neurological samples, such as TBI [57]. Still, elucidating the effect of APOE allelic variation on cognition is important, especially for patients with low grade or benign tumors who are expected to return to daily activities, such as work, that are associated with cognitive fitness [58] after treatment. We identify multiple potential areas of interest for future research. First, although APOE has received most attention in studies on cancer-related cognitive function [59] other genetic polymorphisms should also be recognized and investigated further as potential (interacting) markers for risk of cognitive dysfunction.. For example, COMT and BDNF have been associated with cognition independently [47,60,61] as well as in interaction with APOE genotype.[60,62] Several genes associated with DNA repair, oxidative stress and inflammation have also been described.[59] APOE may also be investigated as a moderating factor for the effect of behavior on cognitive outcomes. For example, longitudinal findings by Ahles and colleagues[51] suggested that the association between APOE and cognition over the course of oncological treatment may be moderated by smoking behavior. In addition, individuals who carry ε2/3 alleles have been reported to benefit more from engaging in complex cognitive activities - as opposed to cognitively less challenging activities - than those who carry ε4.[63] Finally, E4 carrying men with low levels of physical activity appear to be more at risk for cognitive decline as compared to their non-carrying counterparts.[64] Individual brain tumor patients receiving cognitive or physical rehabilitation might benefit to different extents based on APOE genotype.

CONCLUSION

The current prospective longitudinal study was the first to investigate the association between APOE ε4 carrier status and both pre- and post-treatment cognition in patients with primary brain tumors. We found no statistical evidence for a negative effect of ε4 on pre-treatment cognitive performance nor cognitive functioning over time up to 12 months after surgery. Research with larger samples at longer-term follow up and investigations of the potential for APOE to interact with other (genetic) patient characteristics to influence cognitive outcome are warranted.

REFERENCES

1. Ali FS, Hussain MR, Gutiérrez C, et al. Cognitive disability in adult patients with brain tumors. *Cancer Treat Rev*. 2018;65:33-40.
2. Sinha R, Stephenson JM, Price SJ. A systematic review of cognitive function in patients with glioblastoma undergoing surgery. *NeuroOncol Pract*. 2019.
3. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. *Lancet Neurol*. 2004;3(3):159-168.
4. van Kessel E, Baumfalk AE, van Zandvoort MJE, Robe PA, Snijders TJ. Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a systematic review of neurocognitive functioning prior to anti-tumor treatment. *J Neurooncol*. 2017;134(1):9-18.
5. Correa D, DeAngelis L, Shi W, Thaler H, Lin M, Abrey L. Cognitive functions in low-grade gliomas: disease and treatment effects. *J Neurooncol*. 2007;81:175-184.
6. Derks J, Kulik S, Wesseling P, et al. Understanding cognitive functioning in glioma patients: the relevance of IDH-mutation status and functional connectivity. *Brain Behav*. 2019;9(4). https://doi.org/10.1002/brb3.1204
7. Habets EJJ, Hendriks EJ, Taphoorn MJB, et al. Association between tumor location and neurocognitive functioning using tumor localization maps. *J Neurooncol*. 2019.
8. Kaleita T, Wellisch D, Cloughesy T, et al. Prediction of neurocognitive outcome in adult brain tumor patients. *J Neurooncol*. 2004;67:245-253.
9. Noll KR, Sullaway C, Ziu M, Weinberg JS, Wefel JS. Relationships between tumor grade and neurocognitive functioning in patients with glioma of the left temporal lobe prior to surgical resection. *Neuro-Oncol*. 2014;17(4):580-587.
10. Rijnen SJM, Meskal I, Bakker M, et al. Cognitive outcomes in meningioma patients undergoing surgery: individual changes over time and predictors of late cognitive functioning. *Neuro-Oncol*. 2019;21(7):911-922.
11. van Nieuwenhuizen D, Slot KM, Klein M, et al. The association between preoperative edema and postoperative cognitive functioning and health-related quality of life in WHO grade I meningioma patients. *Acta neurochir*. 2019;161(3):579-588.
12. Verghese PB, Castellano JM, Holtzman DM. Apolipoprotein E in Alzheimer’s disease and other neurological disorders. *Lancet Neurol*. 2011;10(3):241-252.
13. Hauser PS, Narayanaswami V, Ryan RO. Apolipoprotein E: from lipid transport to neurobiology. *Prog Lipid Res*. 2011;50(1):62-74.
14. Mahley RW, Huang Y. Apolipoprotein e sets the stage: response to injury triggers neuropathology. *Neuron*. 2012;76(5):871-885.
15. Mahley RW, Weisgraber KH, Huang Y. Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer’s disease. *Proc Nat Acad Sci USA*. 2006;103(15):5644-5651.
16. Tai L, Thomas R, Marottoli F, et al. The Role of APOE in Cerebrovascular Dysfunction. *Acta neuropathol.* 2016;131:709-723.
17. Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapy-induced cognitive changes. *Nat Rev Cancer*. 2007;7(3):192-201.

18. McAllister TW, Ahles TA, Saykin AJ, et al. Cognitive effects of cytotoxic cancer chemotherapy: predisposing risk factors and potential treatments. *Curr Psychiatry Rep.* 2004;6(5):364-371.
19. Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of apolipoprotein E allele ϵ4 with late-onset familial and sporadic Alzheimer's disease. *Neurology*. 1993;43(8):1467-1467.
20. Ballard CG, Morris CM, Rao H, et al. APOEε4 and cognitive decline in older stroke patients with early cognitive impairment. *Neurology*. 2004;63(8):1399-1402.
21. Wagle J, Farner L, Flekkoy K, et al. Association between ApoE epsilon4 and cognitive impairment after stroke. *Dem Ger Cognitive Disord*. 2009;27(6):525-533.
22. Guo Y, Liu F-T, Hou X-H, et al. Predictors of cognitive impairment in Parkinson's disease: a systematic review and meta-analysis of prospective cohort studies. *J Neurol*. 2020 (epub). doi:10.1007/s00415-020-09757-9
23. Ahles TA, Saykin AJ, Noll WW, et al. The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. *Psycho*-Oncol. 2003;12(6):612-619.
24. Koleck TA, Bender CM, Sereika SM, et al. Apolipoprotein E genotype and cognitive function in postmenopausal women with early-stage breast cancer. *Oncol nurs forum.* 2014;41(6):E313-E325.
25. James ML, Blessing R, Bennett E, Laskowitz DT. Apolipoprotein E modifies neurological outcome by affecting cerebral edema but not hematoma size after intracerebral hemorrhage in humans. *J Stroke Cerebrovasc Dis.* 2009;18(2):144-149.
26. Teng Z, Guo Z, Zhong J, et al. ApoE Influences the Blood-Brain Barrier Through the NF-kappaB/MMP-9 Pathway After Traumatic Brain Injury. *Scientific rep*. 2017;7(1):6649.
27. Greenwood PM, Espeseth T, Lin M-K, Reinvang I, Parasuraman R. Longitudinal change in working memory as a function of APOE genotype in midlife and old age. *Scand J Psychol*. 2014;55(3):268-277.
28. Jochemsen HM, Muller M, van der Graaf Y, Geerlings MI. APOE ε4 differentially influences change in memory performance depending on age. The SMART-MR study. *Neurobiol Aging.* 2012;33(4):832.e815-832.e822.
29. Butterfield DA. The 2013 SFRBM discovery award: selected discoveries from the Butterfield laboratory of oxidative stress and its sequela in brain in cognitive disorders exemplified by Alzheimer disease and chemotherapy induced cognitive impairment. *Free Radic Biol Med*. 2014;74:157-174.
30. Froklage F, Reijneveld J, Heimans J. Central neurotoxicity in cancer chemotherapy: Pharmacogenetic insights. *Pharmacogen*. 2011;12:379-395.
31. Jofre-Monseny L, Minihane AM, Rimbach G. Impact of apoE genotype on oxidative stress, inflammation and disease risk. *Mol Nutr Food Res*. 2008;52(1):131-145.
32. Lauderback CM, Kanski J, Hackett JM, Maeda N, Kindy MS, Butterfield DA. Apolipoprotein E modulates Alzheimer's Aβ(1–42)-induced oxidative damage to synaptosomes in an allele-specific manner. *Brain Res*. 2002;924(1):90-97.
33. Mahley RW. Apolipoprotein E: from cardiovascular disease to neurodegenerative disorders. *J Mol Med (Berl).* 2016;94(7):739-746.

34. Villasana L, Acevedo S, Poage C, Raber J. Sex- and APOE Isoform-Dependent Effects of Radiation on Cognitive Function. *Radiat Res*. 2006;166(6):883-891.

35. Correa DD, Satagopan J, Baser RE, et al. APOE polymorphisms and cognitive functions in patients with brain tumors. *Neurology*. 2014;83(4):320-327.

36. Correa DD, Kryza-Lacombe M, Zhou X, et al. A pilot study of neuropsychological functions, APOE and amyloid imaging in patients with gliomas. *J Neurooncol.* 2018;136(3):613-622.

37. Giovagnoli AR, Silvani A, Colombo E, Boiardi A. Facets and determinants of quality of life in patients with recurrent high grade glioma. *J Neurol Neurosurg Psychiatry*. 2005;76(4):562-568.

38. Rijnen SJM, Meskal I, Bakker M, De Baene M, Rutten G, Gehring K, Sitskoorn M. Cognitive outcomes in meningioma patients undergoing surgery: individual changes over time and predictors of late cognitive functioning. *Neuro-Oncol*.21(7);911-922.

39. Rijnen SJM, Kaya G, Gehring K, et al. Cognitive functioning in patients with low-grade glioma: effects of hemispheric tumor location and surgical procedure. *J Neurosurg*. 2019:1-12.

40. Rijnen SJM, Butterbrod E, Rutten G-JM, Sitskoorn MM, Gehring K. Presurgical Identification of Patients With Glioblastoma at Risk for Cognitive Impairment at 3-Month Follow-up. *Neurosurgery*. 2020. https://doi.org/10.1093/neuros/nyaa190

41. Schmand B, Groenink S, Dungen M. Letter fluency: psychometric properties and Dutch normative data. *Tijdschr gerontol geriatr*. 2008;39:64-76.

42. Wechsler D. *Wechsler adult intelligence scale–Fourth Edition (WAIS–IV).* San Antonio, TX: NCS Pearson. 2008;22:498.

43. Rijnen SJM, Meskal I, Emons WHM, et al. Evaluation of Normative Data of a Widely Used Computerized Neuropsychological Battery: Applicability and Effects of Sociodemographic Variables in a Dutch Sample. *Assessment*. 2017:1073191117727346.

44 Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand*. 1983;67(6):361-370.

45. [dataset] Butterbrod E, Sitskoorn M, Bakker M, Jakobs B, Fleischeuer R, Roijers J, Rutten G, Gehring K; 2020; LONG file_APOE; Elisabeth-Tweesteden Hospital.

46. *Linear and Nonlinear Mixed Effects Models* [computer program]. Version R package version 3.1-1452020.

47. Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. *J Stat Software*. 2015, 67(1), 1–48.

48. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: a practical and powerful approach to multiple testing. *J Roy Soc Stat B*. 1995;57(1):289-300.

49. Correa DD, Satagopan J, Martin A, et al. Genetic variants and cognitive functions in patients with brain tumors. *Neuro-Oncol*. 2019;21(10):1297-1309.

50. Greenwood PM, Parasuraman R. Normal genetic variation, cognition, and aging. *Behav Cogn Neurosci Rev.* 2003;2(4):278-306.

51. Ahles TA, Li Y, McDonald BC, et al. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: the impact of APOE and smoking. *Psycho-oncol.* 2014;23(12):1382-1390.

52. Wefel JS, Deshmukh S, Brown PD, et al. Impact of apolipoprotein E (APOE) genotype on neurocognitive function (NCF) in patients with brain metastasis (BM): An analysis of NRG Oncology's RTOG 0614. *J Clin Oncol.* 2018;36(15_suppl):2065-2065.

53. Brown WR, Blair RM, Moody DM, et al. Capillary loss precedes the cognitive impairment induced by fractionated whole-brain irradiation: A potential rat model of vascular dementia. *J Neurol Sci*. 2007;257(1):67-71.

54. Balentova S, Adamkov M. Molecular, Cellular and Functional Effects of Radiation-Induced Brain Injury: A Review. *Int J Mol Sci.* 2015;16(11):27796-27815.

55. Ostrom QT, Cioffi G, Gittleman H, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012-2016. *Neuro-Oncol*. 2019;21(Suppl 5):v1-v100.

56. Shin M-H, Kweon S-S, Choi J-S, et al. The effect of an APOE polymorphism on cognitive function depends on age. *J Neurol*. 2014;261(1):66-72.

57. McFadyen CA, Zeiler FA, Newcombe V, et al. Apolipoprotein E4 Polymorphism and Outcomes from Traumatic Brain Injury: A Living Systematic Review and Meta-Analysis. *J Neurotrauma*. 2019.

58. Mitchell AJ, Kemp S, Benito-León J, Reuber M. The influence of cognitive impairment on health-related quality of life in neurological disease. *Acta Neuropsychiatr.* 2010;22(1):2-13.

59. Buskbjerg CDR, Amidi A, Demontis D, Nissen ER, Zachariae R. Genetic risk factors for cancer-related cognitive impairment: a systematic review. *Acta Oncologica*. 2019; 58:5:537-547.

60. Ward DD, Summers MJ, Saunders NL, Janssen P, Stuart KE, Vickers JC. APOE and BDNF Val66Met polymorphisms combine to influence episodic memory function in older adults. *Beh Brain Res.* 2014;271:309-315.

61. Correa DD, Satagopan J, Cheung K, et al. COMT, BDNF, and DTNBP1 polymorphisms and cognitive functions in patients with brain tumors. *Neuro-Oncol.* 2016;18(10):1425-1433.

62. Martínez MF, Martín XE, Alcelay LG, et al. The COMT Val158 Met polymorphism as an associated risk factor for Alzheimer disease and mild cognitive impairment in APOE 4 carriers. *BMC Neurosci*. 2009;10(1):125.

63. Runge SK, Small BJ, McFall GP, Dixon RA. APOE moderates the association between lifestyle activities and cognitive performance: evidence of genetic plasticity in aging. *J Int Neuropsychol Soc*. 2014;20(5):478-486.

64. Schuit AJ, Feskens EJ, Launer LI, Kromhout D. Physical activity and cognitive decline, the role of the apolipoprotein e4 allele. *MedSci Sports & Exerc.* 2001;33(5):772-777.

3

SUPPLEMENTARY TABLES

Supplementary Table 1 Description of used CNS VS tests

Test	Content	Score computation
CNS VS Verbal Memory (VEM) Test	Fifteen words are presented, one at a time. Subject subsequently identifies presented words among new words by pressing the space bar (immediate and delayed recall).	Total items correct (hits and passes)
CNS VS Visual Memory (VIM) Test	Fifteen abstract images are presented, one at a time. Subject subsequently identifies presented images among new images (immediate and delayed recall).	Total items correct (hits and passes)
CNS VS Symbol Digit Coding (SDC) Test: *Psychomotor speed*	Symbols and corresponding numbers are displayed in the upper part of the screen. Subject matches symbols with correct numbers in a grid on the lower part of the screen for two minutes.	Correct responses – incorrect responses
CNS VS Stroop Test part I (Stroop I): *Simple reaction time*	Part 1: subject presses space bar when a word is presented on the screen. All words describe colors.	Average reaction time correct responses
CNS VS Stroop Test part III (Stroop III): *Inhibitory control*	Part 3: subject presses space bar if the color of the word does not match the meaning of the word (incongruent trials, e.g., the word "green" is presented with a red font).	Average reaction time correct responses
CNS VS Shifting Attention Test (SAT): *Cognitive flexibility*	Subject matches geometric objects by either shape or color to one of two figures in the lower part of the screen for two minutes, using the left and right shift keys. The assignment and figures differ per trial.	Correct responses – Errors
CNS VS Continuous Performance Test (CPT): *Vigilance*	Capital letters are presented on the screen, one at a time. Subject responds to only target letter "B" by pressing the space bar (total test time 5 minutes, uninterrupted).	Average reaction time of responses to target letter

CHAPTER 4

Pre-surgical patterns of cognitive impairment in patients with diffuse glioma revealed by latent class analysis

Submitted

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ABSTRACT

Background Despite the substantial heterogeneity in cognitive performances among glioma patients, studies aiming to elucidate patterns underlying these performances are lacking. Using Latent Class Cluster Analysis (LCA), we investigated 1) subgroups of patients based on patterns in pre-surgical performances across neuropsychological tests, and 2) patient and disease characteristics in relation to group membership.

Methods Glioma patients (n=382, WHO grade II-IV) underwent brief computerized neuropsychological assessment one day before surgery. We selected nine test measures, of which the scores were standardized into Z-scores. We used the dichotomized performances (impaired [Z-score ≤-1.5] versus unimpaired [Z-score >-1.5]) in a bias-adjusted three-step LCA.

Results Cluster 1 illustrated patients with low probabilities of impairment on all tests (n=164).This cluster was characterized by younger age, low mean tumor volume, a high proportion of low grade tumors, and anti-epileptic drug use. Cluster 4 (n=50) illustrated patients with impairment across all tests, and was characterized by a large proportion of high grade and frontal lobe tumors. Clusters 2 (n=81) and 3 (n=64) both showed executive function impairment, but Cluster 3 additionally showed processing and psychomotor slowing and visual memory impairment. Cluster 2 was characterized by younger age and left hemispheric tumors, but Cluster 3 by higher age and high mean tumor volume. Cluster 5 (n=23) showed isolated visual and verbal memory impairment and was characterized by right hemispheric tumors and high mean tumor volume.

Conclusion Subgroups of patients showing distinct pre-surgical cognitive impairment profiles were identified. Routinely obtained characteristics may help to identify patients at risk for specific dysfunctions.

INTRODUCTION

Cognitive dysfunction is an undisputed symptom of diffuse glioma that arises as a result of (the combination of) multiple tumor-related processes.[1-5] It has been shown consistently that executive functioning and memory domains are particularly vulnerable to disruption before treatment.[6-11] Still, deficits can be present in all cognitive domains in varying degrees[5,10] and the number of affected domains varies substantially between patients,[8] indicating considerable inter-individual cognitive heterogeneity. As cognition shapes numerous facets of daily life, such as decision making ability,[12] quality of life [13,14] and interpersonal functioning,[15] an in-depth understanding of the nature of (disease-related) dysfunction is imperative for integrative care.

Approaches to cognitive profiling of glioma patients commonly involve the comparison of (mean) cognitive test performances to normative samples, complemented with the investigation of clinical impairment rates among separate tests and individual patients. A systematic review of 23 studies concluded that about two thirds of the population presents with clinically relevant cognitive impairment prior to treatment.[5] This proportion may be even higher in glioblastoma[3,7,10] as a result of higher lesion momentum.[16-18]

Taking into account the varying rates of impairment in the glioma population,[5,8] as well as the differential interrelations between cognitive functions in general,[19,20] we can expect the large group of patients with cognitive dysfunction to branch off into multiple subgroups of patients showing distinct profiles of cognitive (dys-)function. However, such profiles cannot be revealed by studying tests or domains separately. To adequately understand cognitive heterogeneity glioma patients, research that aims to elucidate patterns in patients' performances across various neuropsychological tests is needed.

By using a clustering approach, as done previously for other cancer-related symptomatology,[21] patient subgroups can be identified based on such underlying patterns. In addition, this method allows us to investigate known patient- and disease-specific correlates of test performances for their value in predicting performance patterns, and thereby help to identify which patients are at risk for which type of dysfunction. Finally, cluster analysis can also reveal to what degree neuropsychological tests contribute to the discrimination between different patterns, and thus their suitability for use in a specific population.

We employed latent class cluster analysis (LCA) to investigate whether distinct subgroups of patients could be identified based patterns in their performances on measures of a computerized neuropsychological test battery. We subsequently explored if group membership was related to patient and disease characteristics that are routinely obtained and largely known at time of diagnosis.

MATERIALS AND METHODS

Study design and data

Data were gathered as part of a prospective longitudinal study in which patients with primary brain tumors undergo neuropsychological assessment (NPA) one day before (T0) and three months after (T3) surgical debulking as part of usual care at the Neurosurgery department of Elisabeth-TweeSteden Hospital (Tilburg, the Netherlands). The project was approved by the local Medical Ethics Committee Brabant (file number NL41351.008.12). Data were used for research purposes with patients' written consent.

For the current study, we used the pre-surgical cognitive data from patients undergoing resection between November 2010 and June 2019 for histologically confirmed diffuse glioma (grade II-IV). Exclusion criteria included age <18, presence of progressive neurological disease, psychiatric or acute neurological disorder within the past two years, and reduced testability (e.g. lack of proficiency in Dutch, estimated premorbid IQ <85). Parts of the current sample have been described previous studies.[11,22-24]

Measures

Sociodemographic

Sociodemographic information including age, sex, educational attainment (categorized into low, middle, and high) was collected via semi-structured interview at the start of the assessment.

Clinical

Information regarding tumor location, anti-epileptic drug (AED) use and corticosteroid use at time of assessment, first resection (versus re-resection), and clinical presentation (symptoms reported at time of diagnosis) were retrieved from the electronic medical charts. Tumor volume before surgery (expressed in cm3) was determined through semi-automatic segmentation (BrainLab Elements25 and ITK-Snap software26) on T1-post contrast enhanced (grade III and IV tumors) or T2-FLAIR series (grade II and III tumors). Histology, grade, isocitrate dehydrogenase type 1 (IDH 1) gene mutation status (wild type vs. mutated), and 1p-19q deletion status (co-deletion vs. no co-deletion) were retrieved from pathological reviews.

Cognitive

We used the computerized Central Nervous System Vital Signs test battery (CNS VS)27 for screening of cognitive functioning. Content of each administered test and the score computations of the nine measures used as indicators are displayed in Supplementary table 1. We used baseline data from CNS VS assessment in healthy controls as described by Rijnen28 for normative purposes. Standardized Z-scores, adjusted for age, sex, and educational attainment, were computed for all valid raw test scores of each patient. The continuous Z-scores were used for descriptive purposes. We dichotomized performances on each test into impairment (Z-score <-1.5; below the 7th percentile based on the control group) or no impairment. Impairment rates were used for both descriptive purposes and as indicators for the main analyses. Re-resection vs first resection candidates were compared with regard to the proportions of impairment on each test with Chi-square tests of independence.

Statistical analyses

Clustering of cognitive data

We performed Latent Class Cluster Analysis (LCA)29 in Latent Gold.30 LCA is a model-based technique that classifies cases into homogeneous groups based on their response patterns on a number of indicators. The underlying assumption is that cases (here: patients) belong to not directly observable (latent) classes. These classes can be seen as subgroups or clusters of patients that are homogeneous with regard to their response patterns (here: their impaired or unimpaired performances on cognitive tests). The assumption of LCA is that the observed responses of patients assigned to the same class arise from the same probability distribution.29 Each patient is assigned a posterior membership probability for each identified cluster. This posterior probability reflects the probability (0-1 scale) of the patient "belonging" to that specific group. Ultimately, each patient is assigned to the group for which they show the highest probability (i.e., their "modal class").

For the LCA, we adopted the bias-adjusted three-step modeling approach developed by Vermunt.31In the first step, we built a latent class model using test performances (impairment vs. no impairment) as indicators and chose the optimal number of latent classes. In the second step, posterior membership probabilities were saved and patients were assigned to classes. In the third step, we predicted posterior membership probabilities with external covariates (predictors) in a multinomial regression while correcting for classification error. The steps are described in detail in below.

Determination of the optimal number of clusters

Due to the lack of theoretical evidence for any number of distinct cognitive classes in the glioma population, we adopted an exploratory approach to determine the optimal number of clusters and performed six separate LCA's of 1 through 6 clusters. We selected the most parsimonious model that also showed the best fit for the data based on a combination of fit statistics. Measures of global fit included: Log-Likelihood (LL), Bayesian Information Criterion (BIC), Akaike Information Criterion (AIC) and model classification error (i.e., the proportion of incorrectly classified cases). We performed statistical comparisons of global fit by testing the difference in log-likelihood between the nested (restricted) and the source (larger) model, e.g. 2-cluster vs. 3-cluster model, using a bootstrapped estimate of the p-value. We used bivariate residuals (BVR) as local indicator of fit[32] and followed the guideline that values higher than 2 indicate that the model at hand cannot explain the association between two indicators[33] and may therefore violate the assumption of local independence. Bootstrapped estimates of the p-values for the BVR in the models were tested against a False Discovery Rate (FDR) corrected alpha level [34] using original α=.05. Classifications of the optimal model were saved to be used for the prediction analysis.

Predicting posterior membership probabilities with external covariates

Latent Gold uses multinomial logistic regression to predict cluster membership probability with external covariates (predictors), while correcting for the model's classification error that can otherwise bias the regression results. External covariates were chosen based on theory[3,4,7,10,35-37] and clinical relevance: age and tumor volume as continuous variables, right vs left hemispheric tumor, non-frontal vs frontal tumor location, non-temporal vs temporal tumor location, low grade vs high grade (histological), IDH-1 wild-type vs mutation, treatment of epilepsy with AED and a clinical presentation that involved cognitive complaints, as dichotomous variables. We also inspected the presence of a nonlinear effect of age[38] by including an age*age interaction. We adopted proportional classification. We used the Maximum Likelihood (ML) method for parameter bias correction, which is recommended for covariates. Cases with missing values any of on the predictors were kept in the model.

RESULTS

Pre-surgical measurements from 444 patients with histopathologically confirmed grade II-IV glioma were identified. Sixty-two patients were excluded from analysis because of medical history or comorbidity (n=17), invalid testing (e.g., due to disorientation, confusion, emotionality or severe fatigue, n=38), technical problems with the laptop (n=1), and early NPA interruption, e.g., the patient completed only the interview or one test after which they expressed the wish to stop (n=6). The final sample comprised 382 patients, see Table 1.

Table 1. Sample characteristics

	Total N = 382	WHO II n=112	WHO III N=38	WHO IV N=232
Age (years) m±SD	53±14	43±13	50±15	58±12
Male	251 (66)	65 (60)	25 (63)	161 (70)
Education				
Low	109 (29)	21 (19)	16 (40)	72 (31)
Middle	128 (33)	38 (35)	12 (30)	78 (33)
High	145 (38)	53 (49)	12 (30)	80 (34)
Re-resection	34 (9)	13 (12)	7 (18)	14 (6)
+ chemo- and radiotherapy	4 (1)	1 (1)	5 (13)	12 (5)
+ chemotherapy only	1 (0)	1 (1)	0 (0)	0
+ radiotherapy only	18 (5)	0 (0)	2 (5)	1 (0)
Histology				
Astrocytoma	326 (85)	64 (58)	29 (72)	233 (100)
Oligodendroglioma	56 (15)	45 (41)	11 (28)	0 (0)
IDH-1 mutated (n=272)	127 (47)	93 (86)	19 (66)	15 (11)
1p/19q co-deleted (n=136)	48 (35)	38 (47)	7 (35)	0 (0)
Frontal lobe involvement†	193 (51)	80 (73)	23 (58)	90 (39)
Temporal lobe involvement†	145 (38)	32 (29)	11 (28)	102 (44)
Parietal lobe involvement†	73 (19)	10 (9)	6 (15)	57 (24)
Occipital lobe involvement†	38 (10)	3 (3)	4 (10)	31 (13)
Lesion hemisphere				
Left	150 (39)	55 (49)	12 (33)	83 (36)
Right	227 (60)	54 (48)	26 (67)	148 (64)
Bilateral	4 (1)	3 (3)	0 (0)	1 (0)
Tumor volume (cm^3) Med, range	37, 1-200	45, 1-200	37, 1-180	35, 1-163
Cognitive complaints at presentation‡	57 (15)	5 (5)	7 (18)	45 (19)
AED use	188 (49)	88 (81)	18 (45)	82 (35)
Corticosteroid use	208 (55)	26 (23)	18 (45)	164 (70)

Values are n(%) unless stated otherwise
† added up percentages may be larger than 100 due to multilobar tumors
‡ reported as a primary symptom at time of presentation

4

Cognitive performances

The mean performance on each test and the proportion of impaired performers are displayed in Table 2. Overall, 25% of patients (n=97) showed no impairment (on any of the tests), 19% (n=73) on one test, and 56% (n=212) on at least two tests. Prevalence of impairment per test ranged from 24% (Verbal memory) to 42% (Stroop task III). Re-resection and first resection candidates did not differ significantly with regard to the impairment proportions on the individual tests (p>.05, data not shown).

Table 2. Pre-surgical cognitive test performances in the total sample

CNS VS test	Mean Z-score ± SD	Impaired performances n (%)
Verbal memory test (VEM, n=363) *Verbal memory*	-0.67 ± 1.31	87 (24)
Visual memory test (VIM, n =375) *Visual memory*	-0.55 ± 1.39	94 (25)
Symbol Digit Coding test (SDC, n =371) *Psychomotor speed*	-0.96 ±1.40	119 (32)
Finger Tapping test (FTT, n =356) *Simple motor speed*	-1.01 ± 1.61	108 (30)
Shifting Attention test (SAT, n =349) *Cognitive flexibility*	-0.91 ± 1.60	113 (32)
Continuous Performance test (CPT, n =375) *Sustained attention*	-0.73 ± 1.64	95 (25)
Stroop test I, reaction time (Stroop I, n =375) *Simple processing speed*	-1.30 ± 2.41	122 (33)
Stroop test III, reaction time (Stroop III rt, n=355) *Executive control; speed*	-1.53 ± 2.35	149 (42)
Stroop test III, correct answers (Stroop III cor n =355) *Executive control; accuracy*	-1.25 ± 2.97	89 (25)

Identification of the number of cognitive clusters in the data

Global fit measures

Supplementary table 2 provides an overview of the investigated models and their evaluative global fit parameters. The 4- and 5-cluster models appeared to be the models that fitted the data best. The 4-cluster model showed a better global fit to the data compared to the 3-cluster model, as indicated by the significant reduction in L2 (conditional bootstrap, *p*=.01, se=.01). The 5-cluster model provided similar AIC and lower LL values compared to the 4-cluster model, but not a significant increase in global fit (*p*=.41, se=.02).

Local fit measures

Inspection of the BVR indicated one value ≥ 2 (relationship SAT – VEM) in the 4-cluster model only. Neither the 4- or 5-cluster model showed significant BVR values under the FDR corrected significance level (p's ≥.01 in both models, α=.001), indicating no significant violation of the local independency assumption. In both models, all test scores significantly contributed to the cluster discrimination (all p's <.05). The variance in test performance explained by the clustering itself (test R^2) ranged between 18% (VEM) and 55% (Stroop I) for the 4-cluster model, and between 23% (FTT) and 56% (Stroop III rt) for the 5-cluster model (data not shown). The most notable difference in explained variance between the 4- and 5- cluster solution was observed for VIM (23% versus 38% respectively). Based on the local fit (BVR values and test R^2) as well as a theoretically relevant additional cluster that was identified in the 5-cluster model (see the Characteristics section), we adopted this model for further analyses. The model is described in detail below.

Characteristics of the 5-cluster model

Table 3 shows the conditional probabilities of impaired and unimpaired performances on each test as well as the overall conditional probabilities (in the total sample). For example, patients in Cluster 1 patients showed a 93% chance of unimpaired performance and 7% of impaired performance on VEM, while the probabilities in the overall sample were 76% and 24% respectively. Probabilities < 0.30 were considered low, 0.30-0.40 low-moderate, 0.40-50 moderate, 0.50 - 0.60 high-moderate and > 0.60 high.

Figure 1 depicts these probabilities in cluster profiles, again indicating how likely patients in each group were to be impaired on the tests. Cluster 1 (n=164, 43% of the total sample) illustrated a "cognitively intact" group with very low chances of impairment on all tests (conditional probabilities ≤0.13), while Cluster 4 (n=50, 13%) was characterized by high chances of impairment on all tests (all conditional probabilities ≥0.6, "global impairment" cluster). Cluster 2 (n=81, 21%) illustrated high-moderate impairment probabilities for SAT and Stroop III reaction time (0.56, 0.51) and low to low-moderate probabilities for the other measures ("executive" cluster). In Cluster 3 (n=64, 17%), we identified high probabilities for Stroop III (both measures) as well as Stroop I impairment (≥0.90), but low-moderate probabilities for SAT impairment (0.38). High-moderate impairment probabilities were present for SDC, FTT and VIM measures, overall indicating a "speed-motor-visual" profile. Cluster 5, the subgroup not revealed in the 4-cluster solution, (n=23, 6%) represented a "memory"-based cluster showing high impairment probabilities for both memory tests (VEM and VIM, >0.70), low-moderate probabilities for psychomotor tasks (SDC and FTT) and low probabilities for all other tasks.

Relationship between cluster membership and external variables

Table 4 provides an overview of the cluster-specific probabilities of the predictors and corresponding parameter statistics. Figure 2 depicts the probabilities in a profile. Age (linear term, Wald =13.1, p=.01; quadratic term, Wald =13.3, p=.01), tumor volume

(Wald =9.0, p=.01), tumor lateralization (Wald =24.2, p<.01), and AED use (Wald=13.0, p=.01) were identified as significant predictors of cluster membership. The following between-cluster differences were observed:

Age. Mean age was significantly lower in Clusters 1 (47.4) and 2 (51.4) as compared to Cluster 3 (64.2; p=.03 and p=.04 respectively).

Tumor volume. Mean tumor volumes (cm3) in Clusters 1 (46.6) and 2 (45.5) were significantly lower than in Clusters 3 and 5 (53.5 and 82.7, p's ≤.02).

Hemisphere. Left hemispheric tumors were most common in Cluster 2 (cluster-specific probability 0.70; 70% of the cluster). This was significantly higher than in all other clusters (p's ≤.01). They were least common in Cluster 5 (3%), this proportion was also significantly lower than in Clusters 1 (43%, p<.01) and 4 (31%, p=.02) respectively. Cluster 3 also contained fewer left hemispheric tumors (14%) compared to Cluster 1 (p=.03).

AED use. Use of AEDs before surgery was highest in Cluster 1 (probability 0.70; 70%) and significantly higher than in Cluster 4 (probability 0.24, p<.01).

Although there was no significant overall effect of the following variables, we observed significant between-cluster differences for frontal tumor location (Cluster 4 > Cluster 2, p=.03), and lesion grade (LGG proportion in Cluster 1 > Cluster 4, p=.048). We found no significant effects (overall or between-cluster comparisons) for temporal involvement, IDH1 gene mutation status or presentation with cognitive complaints (p's >.05).

Table 3. 5-cluster model overview of parameter estimates (R^2 and p-values) and conditional probabilities for each cognitive test in each cluster.

	VEM +	VEM -	VIM +	VIM -	SDC +	SDC -	FTT +	FTT -	SAT +	SAT -	CPT +	CPT -	Stroop I +	Stroop I -	Stroop III rt +	Stroop III rt +	Stroop III cor +	Stroop III cor -
R^2	0.24		0.38		0.29		0.23		0.46		0.41		0.52		0.56		0.48	
p	<.001		<.001		<.001		<.001		.04		<.001		<.001		<.001		<.001	
Cluster 1 n=164 "intact"	0.93	0.07	0.96	0.04	0.92	0.08	0.87	0.13	0.95	0.05	0.93	0.07	0.94	0.06	0.93	0.07	1.00	0.00
Cluster 2 n=81 "executive"	0.76	0.24	0.90	0.10	0.64	0.36	0.80	0.20	0.44	0.56	0.77	0.23	0.79	0.21	0.49	0.51	0.79	0.21
Cluster 3 n=64 "speed-motor-visual"	0.77	0.23	0.47	0.53	0.48	0.52	0.48	0.52	0.62	0.38	0.67	0.33	0.10	0.90	0.09	0.91	0.31	0.69
Cluster 4 n=50 "global"	0.39	0.61	0.41	0.59	0.18	0.82	0.26	0.74	0.01	0.99	0.08	0.92	0.24	0.76	0.03	0.97	0.26	0.74
Cluster 5 n=23 "memory"	0.29	0.71	0.20	0.80	0.67	0.33	0.58	0.42	0.79	0.21	0.99	0.01	0.90	0.10	0.75	0.25	0.92	0.08
Overall n=382	0.76	0.24	0.75	0.25	0.67	0.33	0.69	0.31	0.65	0.35	0.74	0.26	0.67	0.33	0.57	0.43	0.74	0.26

+ refers to unimpaired performance, - refers to impaired performance

Test abbreviations: VEM = Verbal Memory, VIM= Visual memory, SDC = Symbol Digit Coding, FTT=Finger Tapping, SAT= Shifting Attention, CPT= Continuous Performance

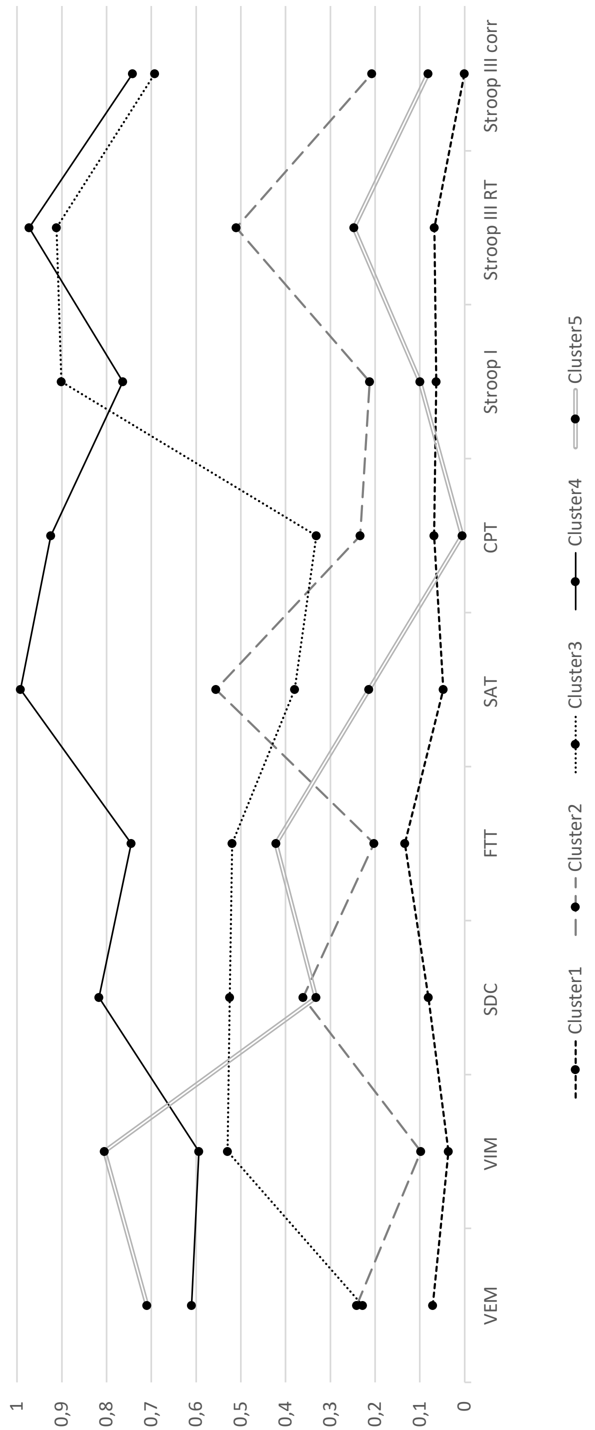

Figure 1. Impairment profiles. Y-axis represents the conditional probabilities of impairment. The x-axis represents (impairment on) the test measures.

Table 4. Bias-adjusted conditional probabilities for external covariates (predictors) per cluster

Covariate	**Cluster**	**1** “intact”	**2** “executive”	**3** “speed-motor-visual”	**4** “global”	**5** “memory”	**Overall**	Wald	*p*
Age	Mean	47.4	51.4	64.2	58.5	51.3	52.8	13.09	.011
Age*Age								13.26	.010
Volume	Mean	46.6	45.5	53.5	51.9	82.7	49.6	9.01	.011
Cognitive complaints	Present	0.06	0.19	0.26	0.22	0.14	0.15	2.38	.67
Hemisphere	Right	0.56	0.29	0.86	0.69	0.97	0.59	15.0	<.01
	Left	0.43	0.70	0.14	0.31	0.03	0.41		
Location	Frontal	0.61	0.40	0.28	0.60	0.65	0.51	6.70	.15
	Temporal	0.32	0.39	0.54	0.35	0.43	0.38	2.78	.60
Grade	II	0.49	0.21	0.03	0.14	0.35	0.29	6.90	.14
	III/IV	0.51	0.79	0.97	0.86	0.65	0.71		
IDH1†	Wild type	0.40	0.67	0.83	0.54	0.56	0.53	2.80	.59
	Mutant	0.60	0.33	0.17	0.46	0.44	0.47		
AED use		0.70	0.42	0.28	0.24	0.46	0.49	13.00	.011

Conditional probabilities refer to probabilities within each cluster, e.g., 70% of patients in Cluster 1 used AEDs as compared to 24% in Cluster 4.
†Proportions for IDH mutation status calculated within non-missing cases

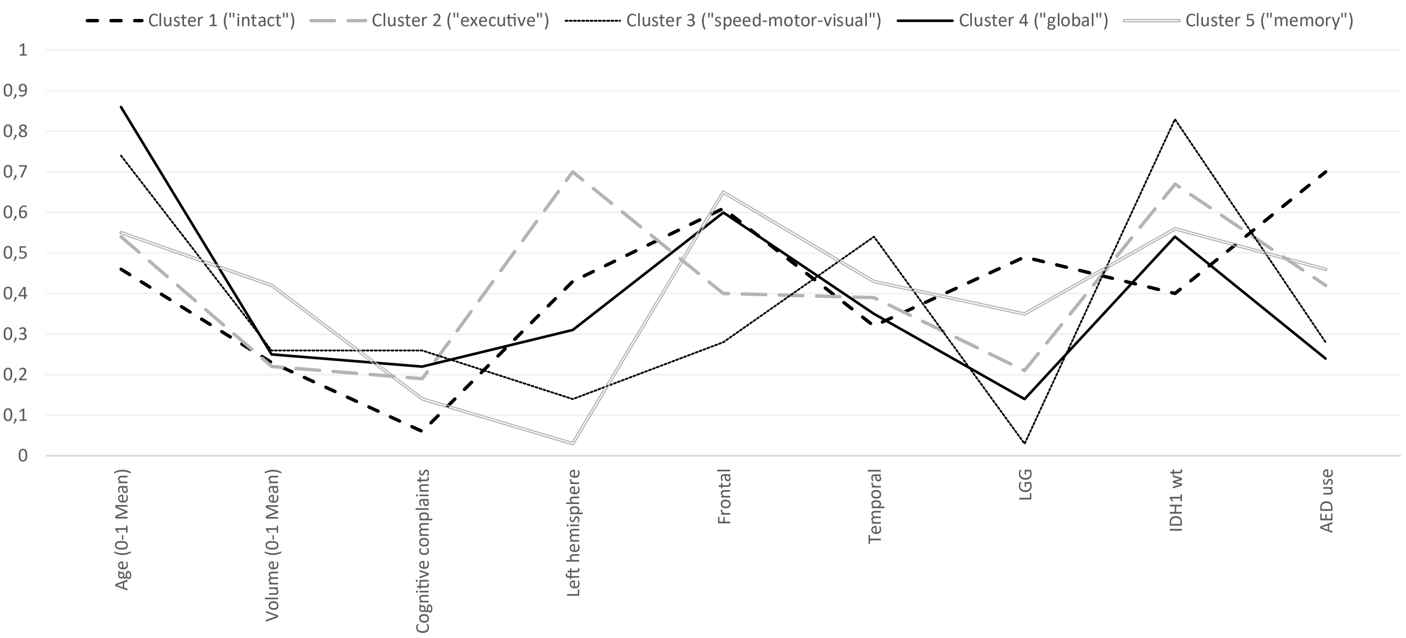

Figure 2. Depiction of conditional probabilities (y) for each predictor (x) per cluster. Continuous variables age and tumor volume were rescaled to a 0-1 scale.

DISCUSSION

To our knowledge, this study is the first to characterize subgroups of glioma patients based on distinct pre-surgical patterns of cognitive impairment with latent class cluster analysis (LCA). Using nine measures of a computerized neuropsychological screening, five groups were identified.

The largest cluster (Cluster 1; 43% of the total sample) consisted of a “cognitively intact” group of patients with low chances of impairment on all tests, irrespective of the cognitive domain. The remaining majority of patients (57%) were, however, assigned to clusters that indicated the presence of varying patterns of clinically relevant dysfunction. In accordance with literature reporting a high prevalence of executive functioning impairment,5 we found particular susceptibility to impairment on such measures in multiple clusters (Clusters 2 and 3). Whereas Cluster 2 patients (21% of the total sample) showed isolated executive dysfunction, Cluster 3 (17%) additionally showed susceptibility to impairment on measures of processing (Stroop part I) and (psycho-)motor speed (Symbol Digit Coding, Finger Tapping) and visual memory. Taking into account that slowed processing speed is more pronounced as tasks become more complex39, and that CNS VS memory tests and Stroop tests all have a time restriction for item presentation, slowing may have been the fundamental problem in this cluster. We found a global pattern of disruption in Cluster 4, indicating that 13% of patients suffered cognitive impairment across the board. Cluster 5 (6%), illustrated a susceptibility to verbal and visual memory impairment only.

All test measures contributed significantly to the discrimination of the clusters. Still, it was evident that the reaction time measures from the Continuous Performance test and Stroop part I, that tap into simple (sustained) attention and processing speed, showed quite low probabilities for impairment on most clusters except those reflecting extensive dysfunction (3 and 4). We also did not find a cluster with isolated impairment on these measures. Based on these findings, a question remains whether the threshold for clinically relevant dysfunction of these more basic functions was only reached if a patient’s cognitive profile was already at a troublesome level (i.e., more complex functions were already disrupted) or if disruption of these functions also disrupted performance on more complex domains.

Multiple patient and disease characteristics showed independent associations with cluster membership. Younger patients (mean age 47.4 years) with low tumor volumes who received treatment for epilepsy characterized the “intact” cognitive phenotype (Cluster 1). Notably, the proportion of high-grade glioma was 51% here, whereas the proportion in the total sample was 71% and in the “globally impaired” Cluster 4 even 86%. The significant difference between Cluster 1 and 4 with regard to high grade tumor proportion supports literature reporting more extensive cognitive disruption with high grade tumors.7 In the current study, the effect was based on histological grading, as IDH1 mutation, in contrast to previous reporting investigating separate test performances,10,16,36 did not reveal predictive value. We note that IDH1 mutation status was only available for 71% of our patients, and this may have led to limited ability to detect a significant (limited) effect. The proportion IDH1 wild-type tumors was relatively high in Cluster 3. The influence of this feature may therefore be restricted to (a limited combination of) specific domains. Cluster 4 was further characterized by a low proportion of patients receiving treatment with AED. Mean age was relatively high (58.5 years) but not significantly different from other clusters. It is worth noting that tumor location measures (hemisphere, frontal and temporal lobe) did not differ significantly between Clusters 1 and 4, that appeared to be at either end of the cognitive spectrum.

Isolated executive impairment (Cluster 2) was associated with low tumor volumes, similarly to “intact” Cluster 1. However, mean age of Cluster 2 (51.4 years) was more comparable to that of the total sample (52.8 years). Cluster 2 presented with a large proportion of left hemispheric tumors (70%, significantly higher than all other clusters), while frontal tumors were less common (40%), in particular compared to the globally impaired Cluster 4. Cluster 3 composition (“speed, motor, visual”) was characterized by older patients (mean 64.2 years) harboring right-sided lesions (86%) with above average volumes. Isolated verbal and visual memory impairment (Cluster 5) was observed in patients with high tumor volumes located in the right hemisphere (97% of this group). High chances of verbal memory impairment along with a high proportion of right hemispheric tumors is a striking finding. In the absence of an empirical lateralization index for verbal ability, we hypothesize that Cluster 5 patients may have been susceptible to a broad memory deficit regarding both verbal and visual information. In contrast, Cluster 3 patients, who also largely harbored right hemispheric tumors, showed vulnerability for dysfunction on the visual memory measure only.

The patient and disease factors that showed independent contributions towards prediction of the clusters have previously also been described as predictors of separate test or domain performance.4,7,8,40-42 However, our findings reveal that some characteristics – patient age, tumor grade, epilepsy treatment - may help to discriminate an intact (Cluster 1) from a broadly impaired (Cluster 3/4) cognitive profile, while others - tumor volume, hemisphere and frontal location – may contribute mostly to discrimination between impaired profiles (Clusters 2-5). We note that, although some factors may be interrelated (e.g., age, AED use, histology), their effects were independent.

We acknowledge several limitations to our current study. First, NPA was integrated into clinical care and combined with hospital admission and MRI one day before surgery. Performing the cognitive screening earlier would be more appropriate for informing patients timely and allowing the clinical team to act on the profile. Still, we believe our results are generalizable to a somewhat earlier time-point, as the prevalence of impairment (overall and on separate domains) were largely comparable to previous reporting5, except for memory, where impairment was less prevalent in our study. We attribute this difference to the test itself rather than timing, because CNS VS memory tests measure immediate and delayed recognition, but not free recall. A second limitation therefore is that, although we did identify a memory cluster in our data, our analyses may still provide an underestimation of the prevalence of memory impairment and may reflect problems with a specific memory sub-modality. Patients at our neurosurgery department undergo assessment as part of standard care unless they have symptoms that impair testability. As we investigated diffuse glioma only, we cannot infer whether the impairment patterns are glioma-specific or if they are also present in CNS tumors with other histopathological features and growth patterns. For example, patients with brain metastases may show more (psycho-)motor impairment43 and patients with meningioma may show a larger “intact” cluster than glioma.44 Finally, we chose a limited number of (cortical) location categories that were believed to be most relevant based on literature, and did not distinguish between degrees of subcortical involvement. Involving subcortical nuclei as well as white matter integrity would fit in a framework of cognitive profiles and could be studied in a larger patient sample.

The current study is explorative and provides new insights into (the prediction of) cognitive profiles in glioma patients that we can gain from non-traditional methods. Our study concerns pre-surgical cognition, but longitudinal clustering applications allow for the estimation of patients’ chances for transitioning from one profile to another profile (i.e, qualitative changes in cognitive functioning) over the course of treatment. In addition, investigating cognitive profiles in relation to other outcomes, such as quality of life,45 and survival outcome, 46 may also give us new information beyond that of individual tests. A main goal to serve clinical practice would be the development and validation of a tool that uses routine patient and disease characteristics to estimate cognitive profiles, as done with previously machine learning in other neurological diseases with a strong cognitive component.47 Clinicians could adapt information provision based on the expected profile, e.g., providing succinct (written) information or involving caregivers in case of isolated memory problems, or taking more time for a consultation in case of speed-related problems, but also to target patients for more elaborate NPA (e.g., adding specific modules to a core assessment battery), specific intra-operative testing during awake surgery, or referral and/or tailoring to/of cognitive rehabilitation in case of a high likelihood of impairment(s).

CONCLUSION

Using tests from a brief computerized cognitive screening, LCA revealed five clusters of glioma patients with different patterns underlying their test performances. Patient and disease characteristics that were predictive of cluster membership can be derived without extensive effort in the consultation room or from diagnostic MRI and are largely known at time of diagnosis. Whereas some patient and disease factors previously related to test performances (age, AED use, lesion grade) seem valuable in distinguishing an “intact” from a (broadly) impaired profile, some factors relating to tumor location (hemisphere, frontal lobe involvement) and tumor volume may be useful mostly for distinguishing different patterns of impairment.

REFERENCES

1. Johnson DR, Wefel JS. Relationship between cognitive function and prognosis in glioblastoma. *CNS Oncol*. 2013; 2(2):195-201.
2. Noll KR, Bradshaw ME, Parsons MW, Dawson EL, Rexer J, Wefel JS. Monitoring of Neurocognitive Function in the Care of Patients with Brain Tumors. *Curr Treat Options Neurol.* 2019; 21(7):33.
3. Sinha R, Stephenson JM, Price SJ. A systematic review of cognitive function in patients with glioblastoma undergoing surgery. *Neuro Oncol Pract.* 2019.
4. Taphoorn MJ, Klein M. Cognitive deficits in adult patients with brain tumours. *Lancet Neurol.* 2004; 3(3):159-168.
5. van Kessel E, Baumfalk AE, van Zandvoort MJE, Robe PA, Snijders TJ. Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a systematic review of neurocognitive functioning prior to anti-tumor treatment. *J Neurooncol*. 2017; 134(1):9-18.
6. Boone M, Roussel M, Chauffert B, Le Gars D, Godefroy O. Prevalence and profile of cognitive impairment in adult glioma: a sensitivity analysis. *J Neurooncol*. 2016; 129(1):123-130.
7. Noll KR, Sullaway C, Ziu M, Weinberg JS, Wefel JS. Relationships between tumor grade and neurocognitive functioning in patients with glioma of the left temporal lobe prior to surgical resection. *Neuro-Oncology.* 2014; 17(4):580-587.
8. Talacchi A, Santini B, Savazzi S, Gerosa M. Cognitive effects of tumour and surgical treatment in glioma patients. J Neurooncol. 2011; 103(3):541-549.
9. Tucha O, Smely C, Preier M, Lange KW. Cognitive deficits before treatment among patients with brain tumors. *Neurosurgery*. 2000; 47(2):324-333;
10. van Kessel E, Emons MAC, Wajer IH, et al. Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a retrospective cohort study prior to antitumor treatment. *Neuro Oncol Pract.* 2019.
11. van Loenen IS, Rijnen SJM, Bruijn J, Rutten G-JM, Gehring K, Sitskoorn MM. Group Changes in Cognitive Performance After Surgery Mask Changes in Individual Patients with Glioblastoma. *World Neurosurg*. 2018; 117:e172-e179.
12. Triebel KL, Martin RC, Nabors LB, Marson DC. Medical decision-making capacity in patients with malignant glioma. *Neurology*. 2009; 73(24):2086.
13. Giovagnoli AR, Silvani A, Colombo E, Boiardi A. Facets and determinants of quality of life in patients with recurrent high grade glioma. *J Neurol Neurosurg Psychiatry*. 2005; 76(4):562-568.
14. Noll KR, Bradshaw ME, Weinberg JS, Wefel JS. Relationships between neurocognitive functioning, mood, and quality of life in patients with temporal lobe glioma. *Psychooncology*. 2017; 26(5):617-624.
15. Giovagnoli AR. Investigation of cognitive impairments in people with brain tumors. *J Neurooncol.* 2012; 108(2):277-283.
16. Derks J, Kulik S, Wesseling P, et al. Understanding cognitive functioning in glioma patients: the relevance of IDH-mutation status and functional connectivity. *Brain Behav*. 2019; 9(4):e01204.
17. Jütten K, Mainz V, Gauggel S, et al. Diffusion Tensor Imaging reveals microstructural heterogeneity of normal-appearing white matter and related cognitive dysfunction in glioma patients. *Front Oncol*. 2019; 9:536.

18. Klein M. Lesion momentum as explanation for preoperative neurocognitive function in patients with malignant glioma. *Neuro-oncology*. 2016; 18(12):1595-1596.

19. Albinet CT, Boucard G, Bouquet CA, Audiffren M. Processing speed and executive functions in cognitive aging: How to disentangle their mutual relationship? *Brain Cogn*. 2012; 79(1):1-11.

20. Perbal S, Couillet J, Azouvi P, Pouthas V. Relationships between time estimation, memory, attention, and processing speed in patients with severe traumatic brain injury. *Neuropsychol*. 2003; 41(12):1599-1610.

21. Miaskowski C, Cooper B, M Paul S, et al. Subgroups of patients with cancer with different symptom experiences and quality-of-life outcomes: a cluster analysis. *Oncol Nurs Forum.* 2006; 33:E79-89.

22. Butterbrod E, Bruijn J, Braaksma MM, et al. Predicting disease progression in high-grade glioma with neuropsychological parameters: the value of personalized longitudinal assessment. *J Neurooncol*. 2019; 144(3):511-518.

23. Rijnen SJM, Butterbrod E, Rutten G-JM, Sitskoorn MM, Gehring K. Presurgical identification of patients with glioblastoma at risk for cognitive impairment at 3-month follow-up. *Neurosurgery*. 2020 (epub); doi: https://doi.org/10.1093/neuros/nyaa190

24. Rijnen SJM, Kaya G, Gehring K, et al. Cognitive functioning in patients with low-grade glioma: effects of hemispheric tumor location and surgical procedure. *J Neurosurg.* 2019:1-12.

25. *Brainlab Elements SmartBrush* [computer program]. Munich, Germany: Brainlab; 2018.

26. Yushkevich PA, Gerig G. ITK-SNAP: an interactive medical image segmentation tool to meet the need for expert-guided segmentation of complex medical images. *IEEE Pulse.* 2017; 8(4):54-57.

27. Gualtieri CT, Johnson LG. Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs. *Arch Clin Neuropsychol.* 2006; 21(7):623-643.

28. Rijnen SJM, Meskal I, Emons WHM, et al. Evaluation of normative data of a widely used computerized neuropsychological battery: applicability and effects of sociodemographic variables in a Dutch sample. *Assessment*. 2017:1073191117727346.

29. Vermunt JK, Magidson, J. *Applied latent class analysis.* In: Applied latent class analysis (pp. 89-106). Cambridge: Cambridge University Press; 2002.

30. *Latent Gold* [computer program]. Version 5.1. Belmont, MA: Statistical Innovations; 2016.

31. Vermunt JK. Latent class modeling with covariates: two improved three-step approaches. *Pol Analysis*. 18(4):450-469.

32. Vermunt JK, Magidson, J. *Technical Guide for Latent Gold 5.1: Basic, Advanced and Syntax.* Belmont, MA: Statistical Innovations; 2013.

33. Schreiber JB. Latent class analysis: an example for reporting results. *Res Soc Admin Pharmacy.* 2017; 13(6):1196-1201.

34. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: a practical and powerful approach to multiple testing. J. *Royal Stat.* Soc 1995; 57(1):289-300.

35. Heimans JJ, Reijneveld JC. Factors affecting the cerebral network in brain tumor patients. *J Neurooncol*. 2012; 108(2):231-237.

36. Wefel JS, Noll KR, Rao G, Cahill DP. Neurocognitive function varies by IDH1 genetic mutation status in patients with malignant glioma prior to surgical resection. *Neuro Oncol.* 2016; 18(12):1656-1663.

37. Habets EJJ, Kloet A, Walchenbach R, Vecht CJ, Klein M, Taphoorn MJB. Tumour and surgery effects on cognitive functioning in high-grade glioma patients. *Acta Neurochir* (*Wien*). 2014; 156(8):1451-1459.

38. Verhaeghen P, Salthouse TA. Meta-analyses of age–cognition relations in adulthood: estimates of linear and nonlinear age effects and structural models. *Psychol Bulletin.* 1997; 122(3):231-249.

39. Keys BA, White DA. Exploring the relationship between age, executive abilities, and psychomotor speed. *J Int Neuropsychol Soc.* 2000; 6(1):76-82.

40. de Groot M, Douw L, Sizoo EM, et al. Levetiracetam improves verbal memory in high-grade glioma patients. *Neuro Oncol*. 2013; 15(2):216-223.

41. Habets EJ, Kloet A, Walchenbach R, Vecht CJ, Klein M, Taphoorn MJ. Tumour and surgery effects on cognitive functioning in high-grade glioma patients. *Acta Neurochir (Wien).* 2014; 156(8):1451-1459.

42. Hendrix P, Hans E, Griessenauer CJ, Simgen A, Oertel J, Karbach J. Neurocognitive status in patients with newly-diagnosed brain tumors in good neurological condition: the impact of tumor type, volume, and location. *Clin Neurol Neurosurg.* 2017; 156:55-62.

43. Schimmel WCM, Gehring K, Hanssens PEJ, Sitskoorn MM. Cognitive functioning and predictors thereof in patients with 1-10 brain metastases selected for stereotactic radiosurgery. *J Neurooncol*. 2019; 145(2):265-276.

44. Meskal I, Gehring K, Rutten G-JM, Sitskoorn MM. Cognitive functioning in meningioma patients: a systematic review. *J Neurooncol.* 2016; 128(2):195-205.

45. Noll KR, Bradshaw ME, Weinberg JE, Wefel J. Relationships between neurocognitive functioning, mood, and quality of life in patients with temporal lobe glioma. *Psycho-Oncol.* 2015;26(5):617-624.

46. Johnson D, Wefel J. Relationship between cognitive function and prognosis in glioblastoma. *CNS Oncol*. 2013; 2:195-201.

47. Pellegrini E, Ballerini L, del C. Valdes Hernandez M et al. Machine learning of neuroimaging for assisted diagnosis of cognitive impairment and dementia: A systematic review. *Alzheimer's Dement (Amst).* 2018;10:519-535.

SUPPLEMENTARY TABLES

Supplementary table 1. Description of neuropsychological tests and their scores used as indicators

Test	Content	Score used as indicator
Verbal Memory (VEM)	Fifteen words are presented, one at a time. Subject subsequently identifies presented words among new words. Delayed recall at end of assessment.	Total items correct for the immediate recall and delayed recall
Visual Memory (VIM)	Fifteen abstract images are presented, one at a time. Subject subsequently identifies presented images among new images. Delayed recall at end of assessment.	Total items correct for the immediate recall and delayed recall
Finger Tapping Test (FTT)	Subject presses space bar as quickly as possible for 10 secs (index finger, three trials per side).	Taps right average + taps left average
Symbol Digit Coding (SDC)	Subject matches symbols presented on the screen with corresponding number for two minutes, using the numbers on the keyboard.	Correct responses – incorrect responses
Stroop Part I (StroopI)	Subject presses space bar when a word is presented on screen.	Average reaction time correct responses Part 1
Stroop Part III (StroopIII)	Subject presses space bar if the color of the presented word does not match the meaning of the word.	*Average reaction time correct responses (StroopIII rt) * Number of correct responses (StroopIII cor)
Shifting Attention Test (SAT)	Subject matches geometric objects by shape or color for two minutes.	Correct responses – Errors
Continuous Performance Test (CPT)	Subject responds to target letter among distractors for 5 minutes.	Average reaction time to target letter

Supplementary table 2. Overview of model characteristics – measures of global fit

	LL	BIC	AIC	Npar	df	Classification error	Entropy R2	Bootstrap L^2 *p* (se)*
2-Cluster	-1683.38	3479.72	3404.75	19	363	0.05	0.82	<.01 (0.00)
3-Cluster	-1665.39	3503.20	3388.78	29	353	0.16	0.65	<.01 (0.00)
4-Cluster	-1650.73	3533.33	3379.45	39	343	0.19	0.65	.02 (0.01)
5-Cluster	-1642.32	3575.96	3382.64	49	333	0.18	0.67	.41 (0.02)

*Comparison of the global fit of the restricted vs larger model, e.g., 2-cluster model compared to the 3-cluster model. P-values are estimated using the bootstrap of L2

CHAPTER 5

Profiles and predictors of cognitive impairment in patients with meningioma before and after surgical resection

Manuscript

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ABSTRACT

Purpose Cognitive dysfunction in patients with meningioma can affect various domains, but it is unclear what specific patterns of dysfunction exist. We performed Latent Class Cluster Analysis (LCA) to identify and predict pre- and postsurgical patterns in performances across neuropsychological tests.

Methods Patients with meningioma underwent computerized neuropsychological assessment one day before (T0, n=402) and three months after (T3, n=347) surgery. Performances on nine test measures were standardized into Z-scores and dichotomized into impaired (Z-score ≤.1.5) and unimpaired (Z-score >-1.5). We performed bias-adjusted three-step LCA's for both time points, using impairment status on the measures as indicators. Patient and disease characteristics were used to predict cluster membership.

Results At T0, we identified four patient clusters showing distinct impairment profiles, which we labelled "cognitively intact", "(psycho)-motor-executive", "executive-processing speed", and "globally impaired". At T3, we identified five clusters that were labelled as "cognitively intact", "verbal memory", "executive-speed" (combining executive, psychomotor and processing speed impairment), "(psycho-)motor-attention", and "diffuse". For both time points, younger age and high education predicted the "intact" profile, and bilateral tumor location predicted multi-domain dysfunction. AED use and location variables (left hemisphere localization, falx, skull base) predicted membership of impaired clusters at T0. Low depressive symptoms predicted the "intact" profile at T3.

Conclusion We identified multiple subgroups of patients characterized by distinct cognitive impairment profiles. Profiles were partly different before versus after surgery, and were related to patient and disease factors. Future studies should further explore the different types of change patients appear to show in their cognitive profiles.

INTRODUCTION

Cognitive functioning is increasingly recognized as a relevant outcome for brain tumor patients undergoing treatment.[1] This is an important development, as cognitive impairment is among the most common symptoms in this population[2-4] and is related to various patient- tumor- and treatment-related factors.[5] The severity of dysfunction in patients with benign tumors, such as meningioma, is reportedly more mild than in patients with malignant tumors characterized by parenchymal infiltration, such as high grade glioma.[6] Still, the majority of meningioma patients suffer from cognitive dysfunction[7,8] that does not necessarily resolve after treatment.[9-11]

The overall cognitive profile of patients with meningioma is heterogeneous, with deficits presenting in various domains. Multiple studies report that dysfunction is most pronounced on measures of executive function and (verbal) memory,[7,8,12,13] whereas others report particular disruption of other functions, such as psychomotor speed.[14-16] These cognitive deficits can interfere with many facets of daily functioning[17-23] and quality of life.[13] Having an adequate understanding of the nature of cognitive dysfunction and being able to predict different dysfunctions is therefore imperative to optimize (shared) decision-making and balance disease and functional outcome for individual patients. Furthermore, it may aid in improving long-term outcomes,[1] such as health care utilization[24] and work performance,[25] on a greater scale.

Studies on cognition in brain tumor patients generally investigate patients' performances on separate tests or domains.[7,8,10-13,15,16,26,27] This approach informs us about the degree to which different cognitive functions are affected before and over the course of treatment. Still, studying performances on cognitive tests or domains separately does not provide an account of which *patterns* exist in patients' performances *across* cognitive domains. In addition, it disregards interrelations between (dysfunction on) domains.[28] In a recent study, we identified five subgroups of glioma patients showing distinct patterns of pre-surgical cognitive impairment across neuropsychological tests with Latent Class Cluster Analysis (LCA).[29] It is still unclear if (such) impairment patterns can be found in patients with other brain tumors, such as meningioma, that show different lesion[26,30] and population[9] characteristics.

Exploring impairment patterns in various PBT population could help to improve peri-surgical and follow-up care. The existence of disease-specific cognitive profiles would warrant tailoring of cognitive monitoring and patient informing within the population. If similar cognitive profiles manifest across diagnoses, a more centralized approach would be appropriate. It is also important to know if cognitive profiles before tumor resection and after tumor resection in the same population are the same or not, i.e., if the type of dysfunction is likely change. In this study we employed LCA to investigate 1) whether meningioma patients could be classified into subgroups based on patterns in their performances across different cognitive tests before and three months after resection, and 2) which patient and disease factors predicted membership of the groups.

METHODS AND MATERIALS

Study design and patients

Data were gathered for the purpose of a prospective longitudinal study in patients with primary brain tumors who undergo neuropsychological assessment (NPA) one day before (T0) and three months after (T3) surgical debulking as part of usual care at the Neurosurgery department of Elisabeth-TweeSteden Hospital (Tilburg, the Netherlands). The study was approved by the local Medical Ethics Committee Brabant (file number NL41351.008.12). Data were used for research purposes with patients' written consent.

We used neuropsychological data from patients undergoing resection between November 2010 and November 2019 for grade I-III infra- or supratentorial meningioma who had completed T0 measurement. Exclusion criteria were age <18, presence of progressive neurological disease, psychiatric or acute neurological disorder within the past two years, and reduced testability (e.g. lack of proficiency in Dutch, estimated premorbid IQ <85). The current sample is described in part in previous studies.[8,9,31]

Measures

Sociodemographic

Age and sex were obtained from electronic medical charts. Educational level (categories: low, middle, high) was obtained by means of a semi-structured interview at the start of the T0 assessment.

Clinical

We obtained the following clinical parameters from the electronic medical charts: tumor grade, symptoms reported by patients at time of diagnosis, use of corticosteroids and anti-epileptic drugs [AED] at T0 and T3, extent of resection assessed with Simpson grade. From symptoms that patients reported at time of diagnosis, we specifically included cognitive complaints for analyses. Tumor localization data were retrieved from surgery reports and categorized first into infratentorial vs. supratentorial location. In case of supratentorial location, further classification included intraventricular, skull base, convexity, parasagittal and falx location. Tumor lateralization contained three categories: left, right, bilateral. Tumor volume (cm^3) was determined through semi-automatic segmentation (BrainLab Elements and ITK-Snap software) on T1-weighted contrast enhanced MRI. Anxiety and depression symptoms were evaluated with the Hospital Anxiety and Depression Scale (HADS) at time of assessment.[32]

Cogntive

We assessed cognitive performances at each time point with the computerized neuropsychological test battery CNS Vital Signs (CNS VS), that is largely based on conventional neuropsychological tests.[33] Assessment with CNS VS covered seven tests (some of which consisting of multiple subtests), took 30-45 minutes and was supervised by a trained test administrator. Supplementary table 1 shows the content of each administered test as well as the score computations of the nine test measures that were used in the analyses. Raw scores were standardized into sex- age- and education-adjusted Z-scores, using data from repeated assessment in our previously obtained sample of healthy controls as reference. Z-scores at T3 were also controlled for practice effects that were demonstrated in the healthy sample.[34] For the main analyses, we dichotomized performances on each test for each individual into impaired (Z-score ≤-1.5; below 6.7th percentile) or unimpaired (Z-score >-1.5). Continuous Z-scores were used for descriptive purposes.

Statistical analyses

Descriptive characteristics were computed in SPSS v24. Latent Class Cluster Analysis (LCA) was performed in Latent Gold[35] v5.1. LCA is a model-based technique that classifies cases (here: patients) into homogeneous subgroups based on their responses on a set of indicators (here: performances on the nine CNS Vital Signs test measures). The underlying assumption of LCA is that cases belong to latent, i.e., not directly observable, classes (clusters), and that the response patterns of cases in the same cluster arise from the same probability distribution.[36] LCA assigns every patient a posterior membership probability for each identified cluster that reflects the probability of the patient "belonging" to that cluster. Every patient is then assigned to the group for which they show the highest probability (i.e., their "modal class"). In the following section, we provide a brief overview of the applied procedure. For a more detailed description, we refer to our previous paper.[29]

5

Three-step approach

We adopted the bias-adjusted three-step approach proposed by Vermunt[37] for the T0 and the T3 data separately. In step 1, we performed six separate LCA's that assumed 1 through 6 clusters, using the nine test performances (impairment vs. no impairment) as indicators, to explore the optimal number of clusters. The estimated models were compared on a combination of global and local fit statistics that are described in detail in our previous study.[29] We calculated an adjusted significance level for analysis of the Bivariate Residuals (BVR) using the approach by Benjamini and Hochberg.[38]

Patients' posterior membership probabilities for each cluster of the optimal model (i.e., the model that was both the most parsimonious model and showed the best fit to the data) were saved, and patients were assigned to their clusters (step 2). Cluster profiles were interpreted based on the conditional probabilities for impairment on the tests. These probabilities reflect the chance of impairment on a measure given membership of a particular cluster. Probabilities < 0.30 were considered low, 0.30-0.40 low-moderate, 0.40-50 moderate, 0.50 - 0.60 high-moderate and > 0.60 high. In step 3, we performed a multinomial multivariate logistic regression to predict cluster membership probability with external covariates (predictors), while correcting for the model's classification error that can otherwise bias results.

External covariates used to predict cluster membership were chosen based on theory[9-11,13,15,39,40] and clinical relevance for each timepoint. T0 candidate predictors included: Age, tumor volume (both as continuous variables), and high (vs low/middle) education, AED use, cognitive complaints reported as a symptom at presentation (vs. no cognitive complaints), atypical (vs. benign) tumor, lateralization (right vs left vs bilateral), and location (infratentorial, convexity, falx, anterior skull base) as categorical variables. T3 candidate predictors included: Age, Hospital Anxiety and Depression Scale Anxiety facet and Depression facet at T3 (as continuous variables), and high education, atypical tumor, lateralization, and location with the same categories as at T0. Lateralization was converted to dummies with right sided lesions as reference group.

Proportional classification was used for the prediction. Parameter bias adjustment was done using the Maximum Likelihood (ML) method.[41] Cases with missing values on the predictor variables were kept in the model. Conditional probabilities (probability of showing a characteristic, given membership of a cluster) were reported for categorical predictor variables and group means for continuous predictor variables.

RESULTS

We identified 466 meningioma patients who underwent T0 measurement as part of regular care and did not meet any of the exclusion criteria. Seventy-seven patients were excluded from the analyses due to invalid or largely incomplete NPA (n=64), e.g., due to motor dysfunction or trouble understanding the instructions, leaving a total of 402 patients of whom data were included at T0. Of this group, fifty-five did not complete T3 assessment. Reasons for dropout included: lost to follow up/no show (n=22), patient cancelled the appointment (n=12), readmission or poor clinical status (n=12), neuropsychological follow-up elsewhere (n=4), patient deceased (n=3), resection cancelled (n=1), patient lived abroad (n=1). Table 1 describes the characteristics of the included samples at T0 and T3. Table 2 shows the mean cognitive test performances and rates of impairment on the tests.

Table 1. Sample characteristics

	T0 N=402	**T3** N=347
Age (years) M±SD, range	57.2±12.1 (23-84)	56.8±11.9 (23-84)
Male, n (%)	109 (27)	91 (26)
Education,		
Low	153 (38)	128 (37)
Middle	118 (29)	101 (29)
High	132 (33)	118 (34)
Previous treatment		
Radiotherapy/radiosurgery	11 (3)	8 (2)
Surgical resection	8 (2)	7 (2)
Embolization	1 (0)	1 (0)
WHO Grade		
WHO I (benign)	370 (92)	321 (92)
WHO II (atypical)	31 (8)	26 (8)
WHO III (malignant)	1 (0)	0 (0)
Lateralization		
Left	164 (40)	143 (41)
Right	190 (48)	163 (47)
Bilateral	48 (12)	41 (12)
Location		
Infratentorial	42 (10)	35 (10)
Intraventricular	7 (2)	6 (2)
Convexity	143 (36)	118 (34)
Parasagittal	19 (5)	15 (4)
Falx	52 (13)	48 (14)
Skull base	159 (40)	145 (42)
Volume (cm3, n=238) Med, range	31.0, 4.5-150.2	31.1, 4.5-150.2
Cognitive complaints at presentation	48 (12)	39 (11)
Anti-epileptic drug use at time of NPA	105 (26)	108 (32)
Extent of resection (n=326)		
Total (Simpson I-III)	n/a	290 (89)
Subtotal (Simpson IV)	n/a	36 (11)

Table 2. Cognitive test performances in the sample at T0 and T3

	T0 n=402		T3 n=347	
CNS VS test†	Mean Z-score ± SD	# Impaired performances (%)	Mean Z-score ± SD	# Impaired performances (%)
Verbal memory test (VEM) (n =387/340)	-0.68±1.34	97 (25)	-0.85±1.39	101 (30)
Visual memory test (VIM) (n =386/342)	-0.50±1.24	78 (20)	-0.32±1.23	60 (18)
Symbol Digit Coding test (SDC) (n =390/339)	-1.07±1.39	138 (35)	-0.81±1.18	81 (24)
Finger Tapping test (FTT) (n =390/341)	-1.00±1.64	135 (35)	-0.62±1.43	73 (21)
Shifting Attention test (SAT) (n =380/329)	-0.98±1.72	127 (33)	-0.81±1.56	84 (26)
Continuous Performance test (CPT) (n =386/341)	-0.57±1.50	76 (20)	-0.81±1.32	84 (25)
Stroop test part I reaction time/rt (n =389/344)	-1.07±2.48	110 (28)	-1.01±2.56	92 (27)
Stroop test part III reaction time/rt (n =381/340)	-1.48±2.27	166 (44)	-1.02±1.76	105 (31)
Stroop test part III correct answers (n =380/338)	-1.49±3.88	88 (23)	-0.30±1.09	20 (6)

† The number of patients with a valid performance at T0/T3 is presented for each test

Identification of the number of cognitive clusters in the data

T0

Global fit measures. Supplementary table 2 shows the global fit statistics for all models (assuming 1 through 6 clusters) of the T0 and T3 data. Global model fit increased significantly from the 2-cluster to the 3-cluster solution (p<.01, Standard Error [SE] = 0.00), and from the 3-cluster to the 4-cluster solution (p=.04, SE=0.01). The 5-cluster model did not show a significantly improved global fit to the data (p=.16, SE=.02) and had a similar class separation (Entropy R^2) and classification error compared to the 4-cluster model.

Local fit measures. We investigated the local fit of the 4-cluster and 5-cluster model. Both did not show significant BVR under FDR corrected α level (.001), data not shown. All of the test measures contributed significantly to the cluster discrimination (all p-values <.01) in both models. The test R^2 (variance in performance on the test explained by the clustering) ranged from 0.14 (VEM) to 0.67 (Stroop IIIrt) for the

4-cluster model and from 0.17 (VEM) to 0.70 (Stroop IIIrt) for the 5-cluster model. Taking into account the similar global and local fit measures, we adopted the 4-cluster solution for the T0 data.

T3

Global fit measures. Global fit of the model increased significantly from the 2- to 3 cluster ($p<.01$, SE=0.00), from the 3- to the 4-cluster solution ($p<.00$, SE=0.00), and from the 4- to 5-cluster solution ($p=.04$, SE=.01). Entropy R^2 was also in favor of the 5-cluster solution (0.83) as compared to the 4-cluster solution (0.67).

Local fit measures. We investigated the local fit of the 4-cluster and 5-cluster model. Only the 4-cluster model showed significant BVR values (relationship FTT-VEM and VIM-VEM, FDR corrected α=.003). Verbal Memory, FTT and Stroop III correct measures did not contribute significantly to the cluster discrimination in the 4-cluster model, *p*'s>.05. In the 5-cluster solution, only the Stroop III correct measure ($p>.05$) did not contribute significantly. R^2 of the tests ranged from 0.11 (VIM) to 0.64 (Stroop IIIrt) for the 4-cluster model, and 0.14 (VIM) to 0.79 (VEM) for the 5-cluster model. Substantial increases in explained variance from the 4- to 5-cluster solution were observed for VEM (0.45 to 0.78 respectively) and FTT (0.17 to 0.44). Based on the global and local fit measures, we adopted the 5-cluster model for the T3 data.

Clusters and profiles of cognitive impairment

T0

Conditional probabilities of impaired performances on each measure per cluster are shown in Table 3 and depicted in Figure 1. For example, patients who were assigned to Cluster 1 showed a 5% (low) chance of impairment on the Symbol Digit Coding test (SDC), while in Cluster 2, patients showed a 73% (high) chance of impairment (conditional probabilities 0.05 and 0.73 respectively).

The cognitive profile of Cluster 1 (n=181, 45% of the sample) was characterized by low conditional probabilities (≤ 0.15) of impairment on all measures, indicating an "intact" cognitive phenotype. Cluster 4 (n=54, 13% of the sample) was characterized by high chances of impairment across all test variables (all conditional probabilities >0.6), except VIM that showed a slightly lower chance (0.56), indicating a "global impairment" cluster. Cluster 2 (n=89, 22% of the sample) showed impairment probabilities >0.50 on SDC and FTT, and probabilities around 0.50 for SAT, and Stroop IIIrt. This cluster was identified as a "(psycho-)motor-executive" phenotype. Cluster 3 (n=78, 20% of the sample) was characterized by very high probability of impairment on Stroop III rt (0.96), high-moderate (0.50) for Stroop III correct measure, and moderate on Stroop Irt (0.40) ("Executive-processing speed" Cluster).

T3

Table 4 and Figure 2 show the conditional probabilities for impairment on the tests per cluster at T3. Similar to T0, we observed an "intact" Cluster 1 (n=172, 50% of the sample) with impairment probabilities < 0.10 for all tests. Cluster 2 (n=58, 17% of the sample) was characterized by isolated VEM impairment (probability 0.96, "verbal memory"). Clusters 3, 4 and 5 showed multi-domain dysfunction. Cluster 3 (n=50, 15%) showed high impairment probabilities (>0.60) for Stroop IIIrt and SAT measures alongside moderate probabilities for SDC and Stroop I, indicating a profile with pronounced executive dysfunction together with psychomotor and processing speed problems ("executive-speed"). A "(psycho-)motor-attention" profile presented in Cluster 4 (n=35, 10% of the sample). This cluster showed particularly high probability for impairment on FTT, and (high-)moderate probabilities (0.41-0.58) for impairment on SDC, SAT and CPT. The most widely impaired cluster (Cluster 5, n=31, 9% of the sample) showed high impairment probability (>0.60) for VEM, and Stroop I and IIIrt, CPT, SAT and SDC. Impairment probabilities for the other measures (FTT, VIM, Stroop III correct), varied from low-moderate to (high-)moderate (0.28-0.56). This cluster was evaluated as a "diffuse" profile without pronounced motor slowing.

Figure 3 depicts the distribution of patients from the T0 clusters over the T3 clusters (for descriptive purposes, no statistical comparisons). As can be seen, the majority (68%) of patients classified in the "intact" Cluster at T0 were classified in the "intact" Cluster at T3, while the other 32% was classified in one of the impairment clusters. Although between 26-38% of patients assigned to an impaired cluster at T0 was assigned to the "intact" cluster at T3, the majority of patients was thus still classified in an impaired cluster at T3.

Table 3. T0: 4-cluster model overview of parameter estimates (R^2 and p-values) and conditional probabilities for impairment per cognitive test in each cluster

	VEM	VIM	SDC	FTT	SAT	CPT	Stroop I rt	Stroop III rt	Stroop III cor
R^2	0.14	0.17	0.52	0.28	0.39	0.29	0.3	0.67	0.53
p	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
Cluster 1 (n=181) "intact"	0.15	0.08	0.05	0.11	0.06	0.02	0.08	0.04	0.01
Cluster 2 (n=89) "(psycho-)motor-executive"	0.24	0.31	0.73	0.56	0.52	0.21	0.26	0.49	0.10
Cluster 3 (n=78) "executive-processing speed"	0.24	0.13	0.25	0.36	0.39	0.30	0.44	0.96	0.50
Cluster 4 (n=54) "global"	0.65	0.56	0.93	0.80	0.92	0.68	0.81	0.99	0.89
Overall (n=402)	0.25	0.2	0.36	0.35	0.34	0.21	0.29	0.45	0.24

Probabilities < 0.30 were considered low, 0.30-0.40 low-moderate, 0.40-50 moderate, 0.50 - 0.60 high-moderate and > 0.60 high

5

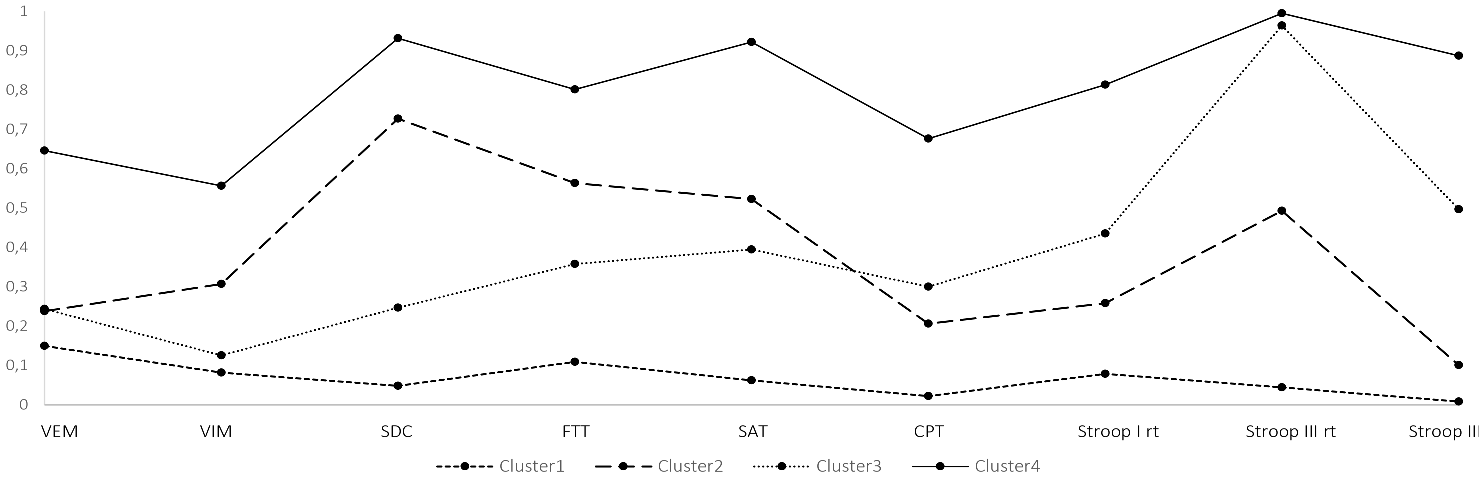

Figure 1. Impairment profiles. Y-axis represents the conditional probabilities of impairment at T0. The X-axis represents (impairment on) the test measures.

Table 4. T3: 5-cluster model overview of parameter estimates (R^2 and p-values) and conditional probabilities for impairment per cognitive test in each cluster

	VEM	VIM	SDC	FTT	SAT	CPT	Stroop I rt	Stroop III rt	Stroop III cor
R^2	0.78	0.15	0.21	0.44	0.34	0.27	0.33	0.63	0.15
p	.03	<.001	<.001	<.01	<.001	<.001	<.001	<.001	.47
Cluster 1 n=172 “intact”	0.01	0.07	0.07	0.08	0.08	0.07	0.10	0.09	0
Cluster 2 n=58 “verbal memory”	0.96	0.29	0.23	0.09	0.11	0.23	0.17	0.1	0
Cluster 3 n=51 “executive-speed”	0.05	0.16	0.47	0.18	0.67	0.32	0.42	0.99	0.17
Cluster 4 n=35 “(psycho-)motor- attention”	0.39	0.20	0.41	0.97	0.44	0.58	0.39	0.26	0.11
Cluster 5 n=31 “diffuse”	0.98	0.55	0.64	0.41	0.72	0.75	0.98	0.94	0.28
Overall n=347	0.30	0.17	0.24	0.21	0.27	0.25	0.27	0.31	0.06

Probabilities < 0.30 were considered low, 0.30-0.40 low-moderate, 0.40-50 moderate, 0.50 - 0.60 high-moderate and > 0.60 high

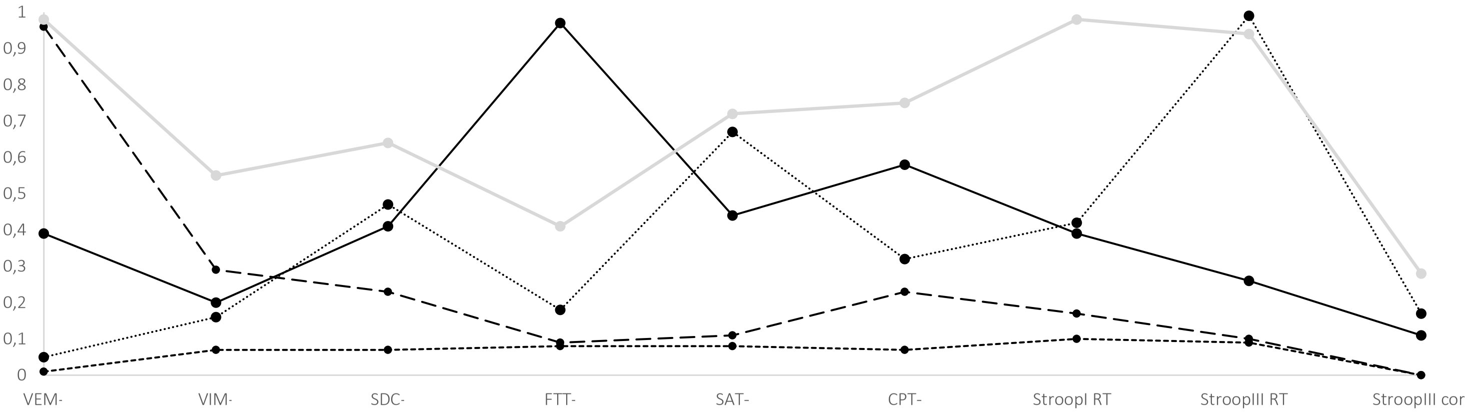

Figure 2. Impairment profiles. Y-axis represents the conditional probabilities of impairment at T3. The x-axis represents (impairment on) the test measures.

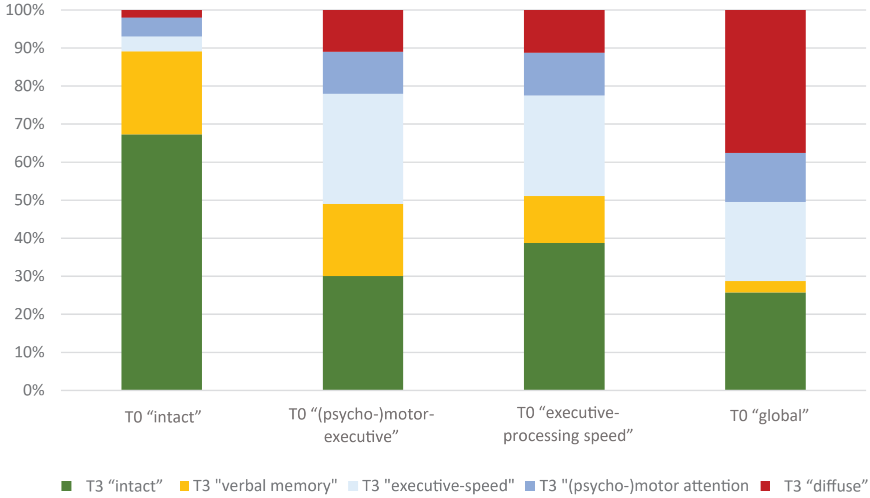

Figure 3. Patient classifications at T3 (stacks), given membership of clusters at T0 (X-axis). E.g., 68% of patients classified in the “intact” cluster at T0 were also classified in the “intact” cluster at T3 (green stack), 22% were classified in the “verbal memory” cluster at T3 (yellow stack), etc.

Prediction of cluster membership

Table 5 shows the results of the prediction analysis for the clusters at pre- and post-surgical assessment (overall predictor effects are presented, effects associated with paired comparisons between clusters are described in the text).

T0

Patient and clinical and variables. Age, high education and cognitive complaints at presentation were significant overall predictors of cluster membership. Paired comparisons revealed that mean age was significantly lower in Cluster 1 (“intact”) as compared to all other clusters (*p*’s <.05). There were no significant differences between Clusters 2 ((“psycho-)motor executive”), 3 (“executive-processing speed) and 4 (“global”). Cluster 1 showed a significantly greater proportion of patients with high education as compared to Cluster 3 and 4 (*p*’s ≤.01), but not Cluster 2. The proportion of cognitive complaints at presentation was lower in Clusters 1 and 2 compared to Clusters 3 and 4 (*p*’s≤.01). Finally, AED use was not an overall significant predictor, but paired comparisons revealed that AED use was significantly lower in Cluster 2 than the other clusters *p*’s<.05.

Tumor-specific variables. Paired comparisons revealed that the proportion of left sided tumors was significantly higher in Cluster 4 as compared to Clusters 1 and 3, *p’s*<.05, and bilateral tumors were more prevalent in Cluster 3 than in Cluster 1, *p*’s≤.01). Tumor volume was significantly lower in Cluster 1 than Cluster 4, *p*=.01. Adhesion to the falx was less common in Cluster 4 than Cluster 1, *p*=.02. Adhesion to the skull base was less common in cluster Cluster 3 than Cluster 1 as well as 4 (*p*=.02 and *p*=.03 respectively).

T3

Patient and clinical and patient variables. Age, high education and HADS depression score were significant overall predictors of cluster membership. Mean age in Clusters 1 (“intact”) and 2 (“verbal memory”) was significantly lower than in Clusters 3 (“executive-speed) and 4 (“(psycho-)motor-attention”), all *p*’s <.05. The proportion of patients with high education was significantly higher in Cluster 1 than all other clusters (*p*’s <.05). Mean HADS Depression score was significantly lower in Cluster 1 than in Clusters 2 and 5 (“diffuse”) *p*’s<.05.

Tumor-specific variables. The proportion of bilateral tumors was significantly higher in Cluster 5 than Cluster 1, *p*<.05). There were no significant effects (overall or between clusters) of any of the other tumor-specific variables.

Table 5. Bias-adjusted conditional probabilities for predictors per cluster identified at T0 and T3

Time point	*T0*							*T3*							
Cluster	1 "intact" n=181	2 "(psycho-) motor executive" n= 78	3 "executive-processing speed" n=89	4 "global" n=54	Overall n=402	Wald	*p*	1 "intact" n= 172	2 "verbal memory" n=58	3 "executive-speed" n=50	4 "(psycho-) motor-attention" n=35	5 "diffuse" n=31	Overall n=347	Wald	*p*
Covariates															
Age	52.6	60.6	60.1	65.9	57.5	22.9	<.01	54.9	53.5	62.3	67.1	61.1	57.5	12.91	.012
High education	0.49	0.26	0.15	0.17	0.33	12.7	<.01	0.48	0.30	0.22	0.06	0.14	0.34	16.88	<.01
Atypical (vs benign)	0.06	0.12	0.09	0.09	0.08	2.1	.56	0.11	0.00	0.05	0.10	0.03	0.11	3.25	.50
Lateralization															
Right (ref)	0.50	0.47	0.49	0.39	0.48			0.46	0.50	0.48	0.54	0.33	0.47		
Left	0.39	0.49	0.29	0.55	0.41	6.01	.11	0.44	0.36	0.39	0.34	0.49	0.41	1.93	.75
Bilateral	0.12	0.04	0.22	0.07	0.12	6.48	.09	0.10	0.14	0.13	0.12	0.18	0.12	5.53	.24
Location															
Falx cerebri	0.14	0.10	0.17	0.08	0.13	5.7	.13	0.15	0.17	0.12	0.09	0.12	0.14	2.57	.63
Convexity	0.27	0.35	0.44	0.51	0.36	2.0	.57	0.35	0.26	0.33	0.27	0.53	0.34	2.17	.70
Skull base	0.48	0.33	0.26	0.45	0.40	6.5	.09	0.42	0.41	0.48	0.52	0.22	0.42	1.52	.82
Infratentorial	0.07	0.26	0.10	0.03	0.10	3.5	.33	0.08	0.17	0.05	0.15	0.14	0.10	5.31	.26

5

Table 5. Continued.

Time point	***T0***							***T3***							
Cluster	1 “intact” n=181	2 “(psycho-) motor executive” n= 78	3 “executive-processing speed” n=89	4 “global” n=54	Overall n=402	Wald	*p*	1 “intact” n= 172	2 ”verbal memory” n=58	3 “executive-speed” n=50	4 “(psycho-) motor-attention” n=35	5 “diffuse” n=31	Overall n=347	Wald	*p*
AED use at NPA	0.28	0.01	0.40	0.26	0.25	3.4	.18	0.32	0.29	0.31	0.28	0.37	0.32	1.13	.89
Cognitive complaints	0.06	0.00	0.22	0.32	0.12	8.5	.02	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Tumor volume	30.6	51.4	33.3	51.6	37.8	2.8	.25	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
HADS Anxiety (M) T3	n/a	n/a	n/a	n/a	n/a	n/a	n/a	4.68	4.11	5.44	5.66	5.79	4.89	4.50	.34
HADS Depression (M) T3	n/a	n/a	n/a	n/a	n/a	n/a	n/a	3.34	3.90	4.52	5.91	5.78	4.08	13.80	<.01

Values of continuous variables (age, tumor volume) represent group means. Values of categorical variables represent conditional probabilities. Conditional probabilities refer to probabilities within each cluster that can be translated into percentages, e.g., probability 0.49 for high education in Cluster 1 means 49% of patients in Cluster 1 had high education.

DISCUSSION

In this study, we performed LCA on neuropsychological test data of patients with meningioma one day before and three months after surgical resection in order to elucidate and predict patterns in (impaired) performances across tests. We identified four patient clusters showing distinct profiles of cognitive impairment at the pre-surgical assessment, and five clusters at the post-surgical assessment.

Clusters before surgery involved two apparently contrasting profiles; an “intact” profile (Cluster 1, 46% of the sample) with low chances of impairment across tests, and a “globally impaired” profile (Cluster 4, 14%), with high chances of impairment across tests. We also observed a “(psycho-)motor-executive” impairment profile (Cluster 2, 18%), with particular susceptibility to impairment on multiple measures of (psycho-) motor and executive function, and a profile characterizing impairment of executive function with additional, although somewhat lower, susceptibility to processing speed impairment (Cluster 3 “executive-processing speed”, 22%).

After surgery, an “intact” profile remained with similar impairment probabilities and cluster size (50%) as the one before surgery. Cluster 2 (17%) appeared as a relatively mild impairment profile, showing a “verbal memory” phenotype with susceptibility only for this measure. There were no separate “(psycho-)motor-executive speed” and “executive-processing speed” clusters after surgery. Rather, Cluster 3 (14%) involved varying degrees of susceptibility to impairment on measures of executive, psychomotor and processing speed in one profile, and was labelled as an “executive-speed” profile. Cluster 4 (10%) involved an apparent “(psycho-)motor-attention” phenotype, where particular motor speed (finger tapping) dysfunction went along with impairment on measures of psychomotor function, shifting attention and sustained attention. Cluster 5 (9%, “diffuse impairment” profile) showed the susceptibility to impairment across most tests, but with relatively spared accuracy on Stroop III (executive measure), visual memory and finger tapping performances.

Patients’ cognitive functioning can be expected to improve after resection, as main drivers of dysfunction, such as intracranial pressure and compression,[7] are relieved. However, stable functioning, (transient) decline in functions and new deficits are also observed.[10,27] The results from the descriptive analysis of the clusters at T0 and T3 support this variance in trajectories on separate tests. For example, two-thirds of patients classified as “intact” at T0 in our study were also classified as “intact” at T3, indicating stable intact performance. One third of the “intact” patients developed some degree of impairment before the three month follow up. Furthermore, 26-38% of patients who were classified to an impaired cluster before surgery (Clusters 2-4) were assigned to the “intact” cluster after surgery. This suggests that, although a portion of patients with an impaired pre-surgical profile showed recovery after surgery, the majority still harbored an impaired profile. Our data also showed change that does not appear to fit in the categories of stability, deterioration or improvement, as some patients appeared to show *a qualitatively different profile* at T3 (e.g., 19% of patients in the pre-surgical “(pyscho-)motor-executive” profile showed an isolated “verbal memory” profile post-surgery).

The contribution of the tests towards profile discrimination were somewhat different at the pre- versus postoperative assessment. Notably, the accuracy measure of Stroop III no longer contributed significantly to discrimination of clusters after surgery. Response speed on the same test did, however, contribute significantly. The explained variance in VEM over time went up from 14% to 78%, probably due to the identification of the isolated verbal memory impairment cluster. From these findings, it seems that sensitivity of tests to detect cognitive profiles may depend on the phase of the disease, especially when we take into account that sample characteristics at both time points were similar. The contribution of various tests to the discrimination of different cognitive profiles should be investigated further in order to determine which tests or domains are useful at different time points.

Several patient, clinical and tumor factors often obtained as part of standard clinical evaluation predicted the clusters. In line with earlier findings on (separate) test performances,[7,42] Cluster 1 (“intact”) was characterized by young age and relatively small tumors before surgery. As much as 50% of patients completed a higher education. In contrast, Cluster 4 (“globally impaired”) had the highest mean age (66 years) of all clusters, and only 17% attained higher education. These two seemingly contrasting profiles were further distinguished by tumor factors and symptomatology; the proportion of left sided lesions, cognitive complaints at time of presentation and mean tumor volume were higher in Cluster 4, while adhesion to the falx was less common. Cluster 2 (“(psycho-)motor-executive”) before surgery was mostly characterized by particularly low proportion of patients reporting cognitive complaints at presentation and low AED use. The exact role of AED use as predictor of this specific cognitive profile is unclear. Based on the known effects of tumor-related epilepsy and its treatment on local and widespread networks underlying cognition,[13] one may expect that AED use would be lowest not in Cluster 2, but the “intact” Cluster 1. AED use in the “intact” and “global impairment” clusters was actually comparable, and similar to the total sample proportion. We hypothesize that patients in Cluster 2 may have had other symptoms at presentation that we did not include in our analysis. Cluster 3 (“executive-processing speed”) comprised a relatively low proportion of patients with high education (15% of the cluster, compared to 33% in the total sample), a low proportion of skull base tumors and a relatively high proportion of bilateral tumors compared to other clusters.

After surgery, the “intact” Cluster 1 was still characterized by young age and a high proportion of patients with high education, but also a low proportion of bilateral tumors, especially compared to Cluster 5 (“diffuse impairment”). In addition, Cluster 1 showed the lowest mean HADS Depression score of all clusters, which is consistent with previous reporting indicating an association between mood and performance on separate cognitive tests[43] that may be mediated by behavioral and biological processes.[44-46] The composition of Cluster 2, with a relatively mild “verbal memory” profile, was mostly comparable to Cluster 1, with the exception of educational level and HADS Depression score. Cluster 5 ("diffuse") harbored a high proportion of bilateral tumors. Although distinguished from the milder clusters 1 and 2, there were no significant differences in characteristics between the clusters with multi-domain impairment (Clusters 3, 4 and 5).

Taken together, younger age and high education seem related to a better cognitive profile before and after surgery, even after correction for their usual effects in the healthy population, whereas bilateral tumor localization appears to be a predictor of multi-domain impairment at both time points. Most tumor localization variables (left hemisphere, falx, skull base) and AED use predicted pre-surgical, but not post-surgical profiles. There are inconsistent findings about whether and which effect meningioma localization has on cognition surrounding or after treatment,[10-12,15] but the current results support the notion that cognition after resection of meningioma may be more related to patient factors[47] that may be static (sociodemographics) or dynamic (depression). At the same time, we also note that, within the localization categories adopted in this study, tumors at specific anatomical sites can invoke different symptoms (e.g., headache in case of sphenoid wing tumors[48], hormonal dysfunction resulting from tuberculum sellae tumors[49]) that may have been differentially related to cognition.

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We observed some notable similarities in the results of the current LCA with our previous findings on pre-surgical impairment profiles in patients with glioma.[29] In particular, it appears that similar percentages of meningioma and glioma patients harbor a cognitive profile without impairment (about 50% of patients) and global impairment (13 % of patients). This finding suggests that the prevalence of (severe) impairment may similar, despite different disease and population characteristics.

We acknowledge limitations concerning our assessment. CNS VS memory tests measure immediate and delayed recognition, but not free recall, and may provide underestimation of memory dysfunction compared to previous research.[7] At the same time, the identification of a "verbal memory" cluster at post-surgical measurement supports previous reporting that a subgroup of meningioma patients show dysfunction on a non-computerized verbal memory test functioning after surgery.[10] Furthermore, as we made a selection of test measures of the CNS VS battery based on clinical relevance, the profiles identified in our study are logically limited these specific measures. Furthermore, we did not adopt mood in the pre-surgical prediction model to preclude overfitting of the model, but we cannot exclude that mood influenced pre-surgical cognition. A second limitation concerns the approach to clustering. We explored the nature of cognitive (dys-)function at different time points. Our results indicate that a portion of patients shifted from one cognitive profile to another, thereby showing a better, worse, or qualitatively different profile after resection. Still, we are limited in our ability to identify *which* patients showed *what type of change* in their profile. Methods exploring latent patterns over time can be of particular value for exploring this issue.

Similar to other illnesses characterized by heterogeneous cognitive phenotypes, e.g., dementia,[50] we may ultimately work towards development of individual risk profiles based on routinely obtained characteristics. A tool like this may improve clinician's ability to anticipate and inform about patients' chances of specific (changes in) cognitive profiles, and to target intervention timely. Since such tools require validation in large clinical cohorts, an opportunity opens up for more collaboration between neurosurgical centers on neuropsychological research. Alongside short-term outcomes, investigations would ideally involve long-term trajectories as well (e.g., one and two years after surgery) where (modifiable) patient characteristics, such as lifestyle factors that have been linked to cognition, such as exercise,[51] may be of interest.

CONCLUSION

About half of meningioma patients showed a cognitive profile with impairment(s) before and after resection. Impairment profiles were partly different for both time points, indicating different natures of cognitive dysfunction. Whereas some patients showed a better or worse cognitive profile after surgery, there was also a subgroup that showed a completely different profile. Tumor localization factors and AED treatment predicted pre-surgical profiles, whereas younger age and high education showed a protective effect against dysfunction both before and after surgery. Low depressive symptoms were related an intact profile after surgery, warranting extra vigilance towards mood disturbances at clinical follow ups. Future studies should further explore the different types of change patients may show in their cognitive profiles over time, and work towards clinically useful prediction tools.

REFERENCES

1. Coomans MB, van der Linden SD, Gehring K, Taphoorn MJB. Treatment of cognitive deficits in brain tumour patients: current status and future directions. *Curr Op Oncol*. 2019; 31(6):540-547.
2. Mukand JA, Blackinton DD, Crincoli MG, Lee JJ, Santos BB. Incidence of neurologic deficits and rehabilitation of patients with brain tumors. *Am J Phys Med Rehabil*. 2001; 80(5):346-350.
3. Fox SW, Mitchell SA, Booth-Jones M. Cognitive impairment in patients with brain tumors: assessment and intervention in the clinic setting. *Clin J Oncol Nurs*. 2006; 10(2):169-223.
4. Tucha O, Smely C, Preier M, Lange KW. Cognitive Deficits before Treatment among Patients with Brain Tumors. *Neurosurgery*. 2000; 47(2):324-334.
5. Taphoorn MJB, Klein M. Cognitive deficits in adult patients with brain tumours. *Lancet Neurol*. 2004; 3(3):159-168.
6. Meskal I, Gehring K, Rutten G-JM, Sitskoorn MM. Cognitive functioning in meningioma patients: a systematic review. *J Neurooncol*. 2016; 128(2):195-205.
7. Bommakanti K, Somayajula S, Suvarna A, et al. Pre-operative and post-operative cognitive deficits in patients with supratentorial meningiomas. *Clin Neurol Neurosurg*. 2016; 143:150-158.
8. Meskal I, Gehring K, van der Linden SD, Rutten G-JM, Sitskoorn MM. Cognitive improvement in meningioma patients after surgery: clinical relevance of computerized testing. *J Neurooncol*. 2015; 121(3):617-625.
9. Rijnen SJM, Meskal I, Bakker M, et al. Cognitive outcomes in meningioma patients undergoing surgery: individual changes over time and predictors of late cognitive functioning. Neuro-Oncology. 2019; 21(7):911-922.
10. Zweckberger K, Hallek E, Vogt L, Giese H, Schick U, Unterberg AW. Prospective analysis of neuropsychological deficits following resection of benign skull base meningiomas. *J Neurosurg*. 2017; 127(6):1242-1248.
11. Dijkstra M, van Nieuwenhuizen D, Stalpers LJA, et al. Late neurocognitive sequelae in patients with WHO grade I meningioma. J Neurol Neurosurg Psychiatry. 2009; 80(8):910.
12. Tucha O, Smely C, Preier M, Becker G, Paul GM, Lange KW. Preoperative and postoperative cognitive functioning in patients with frontal meningiomas. *J Neurosurg*. 2003; 98(1):21-31.
13. Waagemans ML, van Nieuwenhuizen D, Dijkstra M, et al. Long-term Impact of Cognitive Deficits and Epilepsy on Quality of Life in Patients With Low-Grade Meningiomas. *Neurosurgery*. 2011; 69(1):72-79.
14. van Nieuwenhuizen D, Ambachtsheer N, Heimans JJ, Reijneveld JC, Peerdeman SM, Klein M. Neurocognitive functioning and health-related quality of life in patients with radiologically suspected meningiomas. *J Neurooncol*. 2013; 113(3):433-440.
15. Liouta E, Koutsarnakis C, Liakos F, Stranjalis G. Effects of intracranial meningioma location, size, and surgery on neurocognitive functions: a 3-year prospective study. *J Neurosurg*. 2016; 124(6):1578-1584.

5

16. Hendrix P, Hans E, Griessenauer CJ, Simgen A, Oertel J, Karbach J. Neurocognitive function surrounding the resection of frontal WHO grade I meningiomas: a prospective matched-control study. *World Neurosurg*. 2017; 98:203-210.

17. Dreer LE, Devivo MJ, Novack TA, Krzywanski S, Marson DC. Cognitive predictors of medical decision-making capacity in traumatic brain injury. *Rehab psychol*. 2008; 53(4):486-497.

18. Triebel KL, Martin RC, Nabors LB, Marson DC. Medical decision-making capacity in patients with malignant glioma. *Neurology*. 2009; 73(24):2086-2092.

19. Boyle PA, Yu L, Wilson RS, Gamble K, Buchman AS, Bennett DA. Poor decision making Is a consequence of cognitive decline among older persons without Alzheimer's Disease or Mild Cognitive Impairment. *PLOS ONE*. 2012; 7(8):e43647.

20. van der Vossen S, Schepers VP, Berkelbach van der Sprenkel JW, Visser-Meily JM, Post MW. Cognitive and emotional problems in patients after cerebral meningioma surgery. *J Rehabil Med*. 2014; 46(5):430-437.

21. Feuerstein M, Hansen JA, Calvio LC, Johnson L, Ronquillo JG. Work productivity in brain tumor survivors. *J Occup Environ Med*. 2007; 49(7).

22. Fox SW, Lyon D, Farace E. Symptom vlusters in patients With high-grade glioma. *J Nurs Schol*. 2007; 39(1):61-67.

23. Wellisch DK, Kaleita TA, Freeman D, Cloughesy T, Goldman J. Predicting major depression in brain tumor patients. *Psychooncol*. 2002; 11(3):230-238.

24. Xiang X, An R. The Impact of Cognitive Impairment and Comorbid Depression on Disability, Health Care Utilization, and Costs. *Psychiatry Serv*. 2015; 66(11):1245-1248.

25. Collins C, Gehrke A, Feuerstein M. Cognitive tasks challenging brain tumor survivors at work. *J Occup Environ Med*. 2013; 55(12).

26. Cherkil S, Panikar D, Soman DK. Profiling cognitive deficits in intra-axial and extra-axial tumors using Addenbrooke's Cognitive Examination as a screening tool: an indian experience. *Asian J Neurosurg*. 2017; 12(4):653-658.

27. Tucha CSKWLO. Effects of surgery on cognitive functioning of elderly patients with intracranial meningioma. *Br J Neurosurg*. 2001; 15(2):184-188.

28. Lezak MD, Howieson DB, Bigler ED, Tranel D. Neuropsychological assessment, 5th ed. New York, NY, US: Oxford University Press; 2012.

29. Butterbrod E, Schwabe I, Rijnen S, Rutten G, Gehring K, Sitskoorn M. Pre-surgical patterns of cognitive impairment in patients with diffuse glioma revealed by latent class analysis (*In revision*). 2020.

30. Noll KR, Sullaway C, Ziu M, Weinberg JS, Wefel JS. Relationships between tumor grade and neurocognitive functioning in patients with glioma of the left temporal lobe prior to surgical resection. *Neuro-oncology*. 2015; 17(4):580-587.

31. De Baene W, Rijnen SJM, Gehring K, Meskal I, Rutten GM, Sitskoorn MM. Lesion symptom mapping at the regional level in patients with a meningioma. *Neuropsychology*. 2019; 33(1):103-110.

32. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand*. 1983; 67(6):361-370.

33. Gualtieri CT, Johnson LG. Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs. *Arch Clin Neuropsychol*. 2006; 21(7):623-643.

34. Rijnen SJM, Meskal I, Emons WHM, et al. Evaluation of normative data of a widely used computerized neuropsychological battery: applicability and effects of sociodemographic variables in a Dutch sample. *Assessment*. 2017; 27(2):373-383.
35. Vermunt JK, Magidson, J. *Technical Guide for Latent Gold 5.1: Basic, Advanced and Syntax. B*. Belmont, MA: Statistical Innovations; 2013.
36. Vermunt JK, Magidson, J. Latent class cluster analysis. *Applied latent class analysis*. Cambridge: Cambridge University Press; 2002.
37. Vermunt JK. Latent class modeling with covariates: two improved Three-Step approaches. *Pol Analysis*. 18(4):450-469.
38. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J Royal Stat Soc B*. 1995; 57(1):289-300.
39. Steinvorth S, Welzel G, Fuss M, et al. Neuropsychological outcome after fractionated stereotactic radiotherapy (FSRT) for base of skull meningiomas: a prospective 1-year follow-up. *Radiother Oncol.* 2003; 69(2):177-182.
40. Krupp W, Klein C, Koschny R, Holland H, Seifert V, Meixensberger J. Assessment of neuropsychological parameters and quality of life to evaluate outcome in patients with surgically treated supratentorial meningiomas. *Neurosurgery*. 2009; 64(1):40-47.
41. Bakk Z, Vermunt J. *Step-3 Tutorial #1: Step-3 models with covariates, distal outcomes, and multiple latent variables*. 2016:1-18. https://www.statisticalinnovations.com/wp-content/uploads/LGtutorial.Step3_.1.pdf.
42. Kang MJ, Pyun J-M, Baek MJ, et al. Predictors of pre-operative cognitive impairment in meningioma patients over 60 years old. *BMC Neurol*. 2020; 20(1):225.
43. Litofsky NS, Resnick AG. The relationships between depression and brain tumors. *J Neurooncol*. 2009; 94(2):153.
44. Grahek I, Shenhav A, Musslick S, Krebs RM, Koster EHW. Motivation and cognitive control in depression. *Neurosci Biobeh Rev*. 2019; 102:371-381.
45. Keller J, Gomez R, Williams G, et al. HPA axis in major depression: cortisol, clinical symptomatology and genetic variation predict cognition. *Mol Psychiatry*. 2017; 22(4):527-536.
46. Ge R, Torres I, Brown JJ, et al. Functional disconnectivity of the hippocampal network and neural correlates of memory impairment in treatment-resistant depression. *J Aff Disord*. 2019; 253:248-256.
47. Sacks-Zimmerman A, Duggal D, Liberta T. Cognitive remediation therapy for brain tumor survivors with cognitive deficits. Cureus. 2015; 7(10):e350-e350.
48. Bikmaz K, Mrak R, Al-Mefty O. Management of bone-invasive, hyperostotic sphenoid wing meningiomas. *J Neurosurg*. 2007; 107(5):905.
49. Fujio S, Hirano H, Yamashita M, et al. Preoperative and postoperative pituitary function in patients with tuberculum sellae meningioma-based on pituitary provocation tests. *Neurol Med-Chir*. 2017; 57(10):548-556.
50. Jammeh EA, Carroll CB, Pearson SW, et al. Machine-learning based identification of undiagnosed dementia in primary care: a feasibility study. *BJGP Open*. 2018; 2(2):bjgpopen18X101589.
51. Gehring K, Stuiver MM, Visser E, et al. A pilot randomized controlled trial of exercise to improve cognitive performance in patients with stable glioma: a proof of concept. *Neuro-Oncology*. 2019; 22(1):103-115.

SUPPLEMENTARY TABLES

Supplementary table 1. Neuropsychological tests and their scores used as indicators for the LCA's

Test	Content	Score used as indicator
Verbal Memory (VEM)	Fifteen words are presented, one at a time. Subject subsequently identifies presented words among new words. Delayed recall at end of assessment.	Total items correct for the immediate recall and delayed recall
Visual Memory (VIM)	Fifteen abstract images are presented, one at a time. Subject subsequently identifies presented images among new images. Delayed recall at end of assessment.	Total items correct for the immediate recall and delayed recall
Finger Tapping Test (FTT)	Subject presses space bar as quickly as possible for 10 secs (index finger, three trials per side).	Taps right average + taps left average
Symbol Digit Coding (SDC)	Subject matches symbols presented on the screen with corresponding number for two minutes, using the numbers on the keyboard.	Correct responses – incorrect responses
Stroop Part I (StroopI)	Subject presses space bar when a word is presented on screen.	Average reaction time of correct responses Part 1
Stroop Part III (StroopIII)	Subject presses space bar if the color of the presented word does not match the meaning of the word.	*Average reaction time of correct responses Part 3 (StroopIII rt) * Number of correct responses (StroopIII cor)
Shifting Attention Test (SAT)	Subject matches geometric objects by shape or color for two minutes.	Correct responses – Errors
Continuous Performance Test (CPT)	Subject responds to target letter among distractors for 5 minutes.	Average reaction time to target letter

Supplementary table 2. Overview of model characteristics for T0 and T3 data

Model	LL	BIC	AIC	Npar	df	Classification error	Entropy R^2	Bootstrap L^2 *p* (se)†
T0								
2-Cluster	-1776,58	3667,10	3591,17	19	383	0,06	0.79	.00 (0.00)
3-Cluster	-1736,44	3646,77	3530,88	29	373	0,11	0.74	.00 (0.00)
4-Cluster	-1723,45	3680,76	3524,90	39	363	0,16	0.69	.04 (0.01)
5-Cluster	-1713,12	3720,06	3524,24	49	353	0,16	0.71	.16 (0.02)
6-Cluster	-1702,46	3758,70	3522,91	59	343	0,16	0.72	.09 (0.01)
T3								
2-Cluster	-1447,11	3005,36	2932,22	19	328	0,07	0.73	.00(0.00)
3-Cluster	-1431,51	3032,65	2921,01	29	318	0,09	0.75	.00(0.00)
4-Cluster	-1417,30	3062,73	2912,61	39	308	0,17	0.67	.00 (0.00)
5-Cluster	-1405,04	3096,71	2908,09	49	298	0,09	0.80	.04 (0.01)
6-Cluster	-1394,98	3135,07	2907,96	59	288	0,07	0.83	.11 (0.01)

† Comparison of the global fit of the restricted vs larger model. e.g.. 2-cluster model compared to the 3-cluster model. *P*-values are estimated using the bootstrap of L^2

PART III

CHAPTER 6

Cognitive impairment three months after surgery is an independent predictor of survival time in glioblastoma patients

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ABSTRACT

Purpose Cognitive functioning is increasingly investigated for its prognostic value in glioblastoma (GBM) patients, but the association of cognitive status during early adjuvant treatment with survival time is unclear. The aim of this study was to determine whether cognitive performance three months after surgical resection predicted survival time, while using a clinically intuitive time ratio (TR) statistic.

Methods Newly diagnosed patients with GBM undergoing resection between November 2010 and February 2018 completed computerized cognitive assessment 3 months after surgery with the CNS Vital Signs battery (8 measures). The association of cognitive performance (continuous Z-scores and dichotomous impairment status; impaired vs. unimpaired) with survival time was assessed with multivariate Accelerated Failure Time (AFT) models that also included clinical prognostic factors as well as covariates related to cognitive performances.

Results 114 patients were included in the analyses (median survival time 16.4 months). Of the clinical factors, postoperative Karnofsky Performance Status (TR=1.51), surgical (TR=2.20) and non-surgical (TR=1.94) salvage treatment, and pre-surgical tumor volume (cm^3, TR=1.003) were significant independent predictors of survival time. Independently of the base model factors and covariates, impairment on Stroop test I and Stroop test III estimated 23% and 26% reduction of survival time (TR=0.77, TR=0.74) respectively, as compared to unimpaired performance.

Conclusion These findings suggest that impaired performances on tests of executive control and processing speed in the early phase of adjuvant treatment can reflect a worse prognostic outlook rather than an early treatment effect, and their assessment might allow for early refinement of current prognostic stratification.

INTRODUCTION

To date, functional performance status (PS) appears to be one of the few clinical factors consistently allowing for prognostic stratification in the glioblastoma (GBM) population.[1-3] Despite methodological issue ,[4,5] it has shown superior predictive value compared to characteristics such as macroscopic extent of resection[1] and patient age.[3,6] Still, prognostic heterogeneity remains within clinically defined risk groups[7] and identification of other patient-related markers could advance clinical monitoring and decision-making.

Measures tapping into functional domains that underlie PS, such as fatigue and cognitive functioning, have been evaluated increasingly for their prognostic value in glioma.[8,9] Poorer cognitive performance in treatment- naive patients appears to predict worse survival outcome.[10,11] However, not all patients can be tested (validly) in the short period between diagnosis and start of treatment, and although pre-treatment cognitive dysfunction may reflect tumor status,[9,12] its nature or severity may be affected by distress from the diagnosis[9,13] tumor laterality,[14] or motor symptoms.[12,13]

After commencement of anti-tumor treatment, the overall cognitive profile of GBM patients remains characterized by high levels of impairment.[15] Multiple investigations have explored the significance of post-surgical cognitive (dys-)function for survival, mostly by targeting cognitive assessment between surgical debulking and start of (chemo-)radiation. These studies have suggested a contribution of (impaired) cognitive performance, especially executive functioning, to the estimation of hazard rates in (older) patients.[16-20] It remains unknown, however, whether cognitive status during early adjuvant treatment with radio- and/or chemotherapy bears value in predicting survival outcome.

Furthermore, although the commonly reported hazard ratio(HR)[10,17-20] statistic provides information about the rates of death during follow up among patients with different cognitive performances, it does not directly translate into an estimation of differences in survival time. Considering the poor prognosis associated with GBM, readily interpretable information about survival duration can be of particular interest to clinicians. The accelerated failure time model (AFT)[21] allows for the immediate derivation of a time ratio (TR) that indicates if a variable is related to shorter or longer survival time, e.g., in months, which is arguably more clinically intuitive.

The current study employed AFT modeling to investigate whether cognitive performance three months after surgical resection predicts survival time in GBM patients, with the aim of contributing to our understanding of the prognostic value of cognitive performance during adjuvant treatment and early refinement of prognostic models.

MATERIALS AND METHODS

Design

Data was obtained as part of a prospective longitudinal study in which patients with primary brain tumors underwent neuropsychological assessment (NPA) one day before (T0) and three months after surgery (T3) as part of usual care at Elisabeth-TweeSteden Hospital (Tilburg, the Netherlands). This study was approved by the local Medical Ethics Committee Brabant (file number NL41351.008.12).

Patients

For the current study, patients who underwent surgical resection of histopathologically confirmed GBM between November 2010 and February 2018, and who completed NPA at T3 were considered for inclusion. All included patients provided written informed consent. We excluded patients if at least one of the following criteria was met: age <18, diagnosis of a progressive neurological disease, psychiatric or acute neurological disorder within the past two years, previous intracranial surgery, or impaired testability (e.g., lack of proficiency in Dutch, estimated IQ <85, serious visual or motor deficits). Part of the current sample has been described previously.[15,22]

Cognitive functioning

We measured cognitive performance with a computerized neuropsychological test battery (CNS Vital Signs, CNS VS).[23] Content of the tests that were used are displayed in Supplementary Table 1. Test validity was evaluated by the test administrator at time of testing and documented in a separate observation document. Invalid test performances were excluded. We used data from repeated assessment with CNS VS in healthy controls[24] for normative purposes. Based on these data, we computed Z-scores that were adjusted for age, sex and educational attainment for each test performance (M=0, SD=1). A Z-score ≤-1.5 (performance below the 7th percentile) was considered impaired, and Z-score between -1 and -1.49 (performance between 7th and 16th percentile) was considered low. Valid scores were not truncated. The proportion of impaired performances relative to number of valid test scores per patient ($\frac{\#\ impaired\ performances}{\#\ valid\ tests}$) was calculated for descriptive purposes.

Clinical measures

We retrieved the following data from the electronic medical charts: tumor location, macroscopic extent of resection, KPS, anti-epileptic drug (AED) use, corticosteroid use, adjuvant treatment protocol, salvage treatment, and treatment-related events (e.g., allergic reaction, infection, thrombocytopenia). Isocitrate dehydrogenase type 1 (IDH1) gene mutation status was retrieved from pathological reports. We determined presurgical tumor volume (expressed in cm^3) through semi-automatic segmentation with BrainLab Elements Smartbrush or ITK-Snap software on T1-post contrast-enhanced series.

Statistical analyses

Survival time

Survival time was defined as the time between debulking and either date of death or last known contact before February 1st 2019 (in months). A survival curve displaying the proportion of patients surviving as a function of time was plotted.

Cognitive performance

We compared the mean performances of patients on each test to that of healthy controls with Z-tests.

Accelerated failure time models

We used the Accelerated Failure Time (AFT) model to investigate differences in survival time between groups. The AFT model provides a baseline survivor function and an acceleration coefficient that indicates whether a covariate "accelerates" or "decelerates" time until death. The exponentiated coefficient constitutes a time ratio (TR). TR<1 or TR>1 indicates that a variable is related to shorter or longer survival time respectively, e.g., a TR of 0.70 means that patients with a certain characteristic are estimated to have a median survival time that is 70% of patients without that characteristic.

Data distribution. We fitted models that assumed different distributions (Exponential, Weibull, Lognormal, Log-logistic, Gamma and Gauss). The model that fitted the data best, while being parsimonious, was selected based on a comparison of fit statistics (Akaike Information Criterion, AIC).

Base model. An initial base model included known clinical predictors of survival, including age at time of surgery, pre-surgical tumor volume (cm^3), extent of resection (macroscopic total vs subtotal), KPS (at T3) (≤ 80 vs 90-100), adjuvant treatment protocol (chemoradiation vs other), treatment-related events, and salvage therapy (none [as reference category], non-surgical, surgical). We kept variables that significantly predicted survival time (α=.05) in the base model.

Cognitive models. We added the performances on the tests (continuous Z-scores and dichotomous impairment status; not impaired vs. impaired) to the base model separately. Before running the cognitive models, we investigated potential covariates (clinical and sociodemographic variables that differed between impairment groups or were related to the Z-scores) : sex, low educational level, high educational level, affected hemisphere, frontal involvement, corticosteroid use at T3, AED use at T3, and the clinical factors that were not significant predictors in the base model. Covariate analyses included ANOVA's and (non-)parametric correlations (Z-scores), in addition to independent samples t-tests and Chi-Square tests (impairment status). If significantly related to the test performance (α=.05), the covariate was added to the AFT model containing the relevant cognitive test score. We performed multiple testing corrections with the False Discovery Rate procedure by Benjamini and Hochberg [25] (separate corrections for the Z-score models and the impairment models).

Multivariate estimation of median time to event (MTTE). For a direct comparison of survival probabilities of patients who showed similar clinical characteristics, but different cognitive performances, we computed estimations of MTTE for the significant models and their predictors. Survival curves were plotted to visualize survival differences over time.

Analyses were conducted in SPSS Statisics v.24 and Rstudio, using the survival[26] package.

RESULTS

Sample

One hundred and fourteen patients with T3 data were included in the analyses (see Supplementary Figure 1 for a flowchart, including reasons for dropout before T3 and exclusion). Table 1 displays the sample characteristics.

Cognitive functioning

Average time between surgery and T3 measurement was 3.03 months (95% CI 2.95–3.12 months). Table 2 provides group performances (mean Z scores) and impairment counts for all tests at T3. The number of valid performances ranged between n = 107 and n = 113. Invalid performances were the consequence of technical problems during a test, external distraction, not understanding or repeatedly forgetting the instructions of a test, color blindness (Stoop test III and Shifting Attention test only) and mild unilateral motor disturbances (Finger Tapping test and Shifting Attention test only).

Eighty-seven percent (n = 99) of patients displayed some degree of impairment (on at least one of the tests they completed); 38% (n = 43) on less than one third of the tests, 16% (n = 18) on at least one third, but less than half of the tests, and 33% of patients (n = 38) showed impairment on at least half of the tests.

Table 1. Patient characteristics

	N=114
Male	83 (73%)
Age at time of surgery (m±SD, range)	58±12, 18-80
Educational level	
Low	38 (33%)
Middle	43 (38%)
High	33 (29%)
Tumor volume (cm^3) Median (range)	35 (1-163)
Tumor lateralization	
Right	68 (60%)
Left	46 (40%)
Frontal involvement	41 (36%)
IDH1 wild-type n=66)	62 (94%)
KPS at T3† (n=111)	
80 or below	32 (29%)
90-100	79 (71%)
AED use at T3 (n=111)	41 (37%)
Corticosteroid use at T3 (n=113)	46 (41%)
Macroscopic extent of resection	
Gross total (<90%)	70 (61%)
Gross subtotal (>90%)	44 (39%)
Adjuvant treatment‡	
Chemoradiation (followed by TMZ monotherapy)	104 (91%)
Radiotherapy only	9 (8%)
No adjuvant treatment	1 (1%)
Treatment-related event	12 (11%)
Salvage therapy (n=113)	
No salvage therapy	62 (55%)
Non-surgical (e.g., TMZ, lomustine, XRT)	29 (26%)
Surgical (with or without additional treatment)	22 (19%)

Values presented n (%) unless stated otherwise

† ECOG/WHO functional status instead of KPS was reported for 6 patients. This score was converted to KPS (ECOG 0 = KPS 90-100, ECOG 1 = KPS 80 or below).TMZ= temozolomide

‡ all patients had started adjuvant treatment before T3 NPA

6

Table 2. Mean cognitive test scores (group level) and impairment counts

CNS VS test	Mean Z-score	# Impaired performances†	# Low performances‡	# Normal performances§
Verbal memory test (VEM) (n=109)	-0.82 ± 1.27**	33 (30%)	13 (12%)	63 (58%)
Visual memory test (VIM) (n =111)	-0.52 ± 1.04**	18 (16%)	22 (20%)	71 (64%)
Symbol Digit Coding test (SDC) (n =112)	-1.17 ±1.27**	46 (41%)	14 (13%)	52 (46%)
Finger Tapping test (FTT) (n =112)	-0.94 ± 1.53**	34 (31%)	16 (14%)	62 (55%)
Shifting Attention test (SAT) (n =107)	-1.37 ± 1.79**	42 (39%)	10 (9%)	55 (52%)
Continuous Performance test (CPT) (n =113)	-1.32 ± 2.59**	39 (35%)	16 (14%)	58 (51%)
Stroop test part I (n =112)	-1.66 ± 2.78**	47 (42%)	5 (4%)	60 (54%)
Stroop test part III (n =109)	-1.77± 1.93**	56 (51%)	11 (10%)	42 (39%)

† Z-score ≤-1.5, ‡ -1.49 ≤ Z-score ≤-1, § Z-score ≥ -0.99
** Significant difference from healthy control group (Z-tests, *p*<.001)

Survival

The lognormal distribution provided the lowest AIC among the tested models, indicating the best fit for the data. Figure 1 displays the survival probability over time (no predictors). The median survival time was 16.4 months (95% CI 13.90–18.85). At the defined time-point, 91 of 114 patients were deceased (79.8%).

Base model

Of the included clinical variables, T3 KPS of 90–100 (p < 0.001), salvage therapy (non-surgical and surgical) (*p*'s < 0.001), and pre-surgical tumor volume (*p* = 0.02) were significant positive predictors of survival time (TR= 1.51, 1.94, 2.20, and 1.003 respectively). Age, extent of resection, adjuvant treatment protocol, and treatment-related events were not related to survival time (*p*'s > 0.05).

Cognitive model—continuous Z-scores

Based on analyses of the covariates, we adopted the following variables as covariates in the cognitive models: age at time of surgery (SDC, SAT, Stroop I, Stroop III), sex (SAT), right hemispheric tumor (VIM), and corticosteroid use at T3 (FTT). None of the eight continuous Z scores showed a significant independent relationship with survival time under the adjusted alpha level after B–H correction (α = 0.006; see Table 3). None of the included covariates showed a significant independent contribution to prediction of survival time.

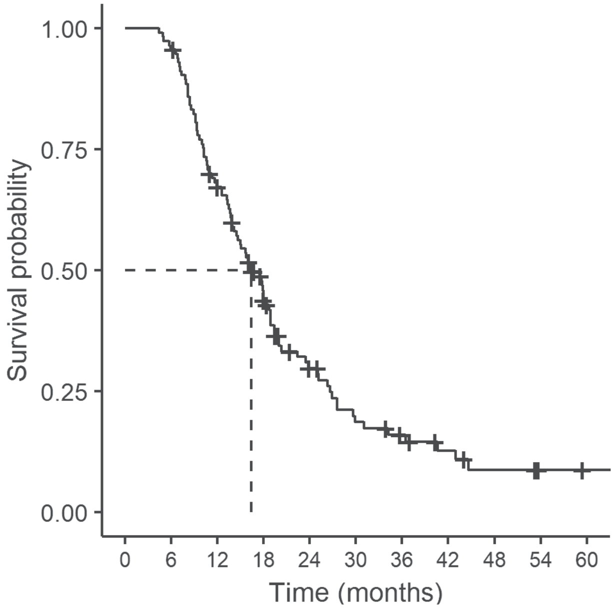

Figure. 1 Survival probability over time and estimated median survival time (censoring is indicated with +)

Cognitive status—impairment

Covariates for impairment status included age at time of surgery (SDC, Stroop I, Stroop III), sex (VIM), low educational level (SDC), right hemispheric tumor (Stroop I), corticosteroid use at T3 (VEM), extent of resection (VIM), and frontal involvement (CPT). Salvage treatment was significantly associated with less SDC, SAT, Stroop I and Stroop III impairment ($p < 0.05$), but was already part of the clinical model. As shown in Table 3, addition of impairment status and relevant covariates to the base model showed that impaired performance on Stroop I (p < 0.01, TR = 0.77) and Stroop III ($p < 0.01$, TR = 0.74) were independent negative predictors of survival time (i.e., decreasing survival duration) under the adjusted alpha level ($\alpha = 0.013$). Tumor volume was not an independent predictor for survival time in the Stroop I and III models ($p > 0.013$), while KPS and salvage treatments remained significant (p's < 0.01). None of the covariates showed a significant contribution to the prediction of survival time.

Table 3. Multivariate analyses of cognitive performances and survival time

Variable	Coefficient (95% CI)	SE	TR	*p*	Model AIC
Base model					
KPS 90-100 at T3 (vs. ≤ 80)	0.41 (0.21-0.64)	0.11	1.51	<.001	614.3
Salvage treatment (vs. none)					
Surgical	0.78 (0.53-1.04)	0.13	2.20	<.001	
Non-surgical	0.66 (0.45-0.91)	0.12	1.94	<.001	
Volume (expressed in cm^3)	0.003 (-0.001-0.005)	0.001	1.003	.02	
Cognitive model – Z-scores					
Z-score VEM	0.05 (-0.02-0.12)	0.04	1.05	.14	585.2
Z-score VIM†	-0.02 (-0.11-0.08)	0.05	0.98	.71	599.2
Z-score SDC†	0.08 (0.00-0.16)	0.04	1.08	.06	602.3
Z-score FTT†	0.02 (-0.05-0.07)	0.01	1.01	.68	599.1
Z-score SAT†	-0.01 (-0.06-0.05)	0.03	0.99	.73	578.4
Z-score CPT	0.01 (0.00-0.03)	0.02	1.01	.72	607.2
Z-score Stroop I†	0.01 (-0.02-0.04)	0.02	1.02	.53	610.1
Z-score Stroop III†	0.06 (0.00-0.11)	0.03	1.06	.03	590.7
Cognitive model – Impairment					
Impairment VEM†	-0.19 (-0.39-0.00)	0.10	0.83	.07	577.0
Impairment VIM†	0.15 (-0.12-0.42)	0.13	1.17	.24	600.2
Impairment SDC†	-0.13 (-0.33-0.06)	0.10	0.88	.19	603.6
Impairment FTT	-0.11 (-0.29-0.11)	0.10	0.90	.30	604.1
Impairment SAT†	0.06 (-0.12-0.27)	0.09	1.07	.52	579.6
Impairment CPT†	-0.11 (-0.30-0.08)	0.10	0. 90	.28	607.4
Impairment Stroop I†	-0.26 (-0.46--0.08)	0.10	0.77	<.01	603.2
Impairment Stroop III†	-0.31 (-0.48--0.09)	0.10	0.74	<.01	586.3

† model contained covariate(s), see Results section
SE=Standard error, TR = Time Ratio

Multivariate estimation of median time to event (MTTE)

We estimated survival probabilities for patients with similar clinical characteristics, but different impairment status, using the predicted covariance matrices of all significant variables in the Stroop I and Stroop III models. For example, a comparison is shown below of patients with KPS 90–100 (n = 79) who did not receive salvage therapy after progression, and either did show impairment (i.e., survival probability for patient 1, denoted by p1) or not (i.e., survival probability for patient 2, denoted by p2).

p1 = (KPS at T3=90-100, salvage therapy=none, cognitive status = impaired)
p2 = (KPS at T3 =90-100, salvage therapy=none, cognitive status = unimpaired).

Stroop III test

Estimated MTTE for p1 was 12.1 months, compared to 16.1 months for p2, reflecting an estimated shorter survival time of 4.0 months for the impaired performer.

Stroop I test

Estimated MTTE for p1 was 12.3 months, compared to 15.9 months for p2, reflecting an estimated shorter survival of 3.6 months for the impaired performer.
We repeated this procedure for patients with KPS 90–100, who received non-surgical salvage therapy (MTTE = 22.8 vs 30.5 months for Stroop III impaired vs. unimpaired performers, 22.5 vs. 28.9 months for Stroop I impaired vs. unimpaired performers), and surgical salvage therapy (MTTE = 23.7 vs. 31.7 months for Stroop III impaired vs. unimpaired performers, 24.2 vs. 31.2 months for Stroop I impaired vs unimpaired performers). See Figure 2 for multivariate survival plots for the described scenarios. We did not perform estimations for patients with KPS ≤ 80 (n = 32) due to the lower sample size.

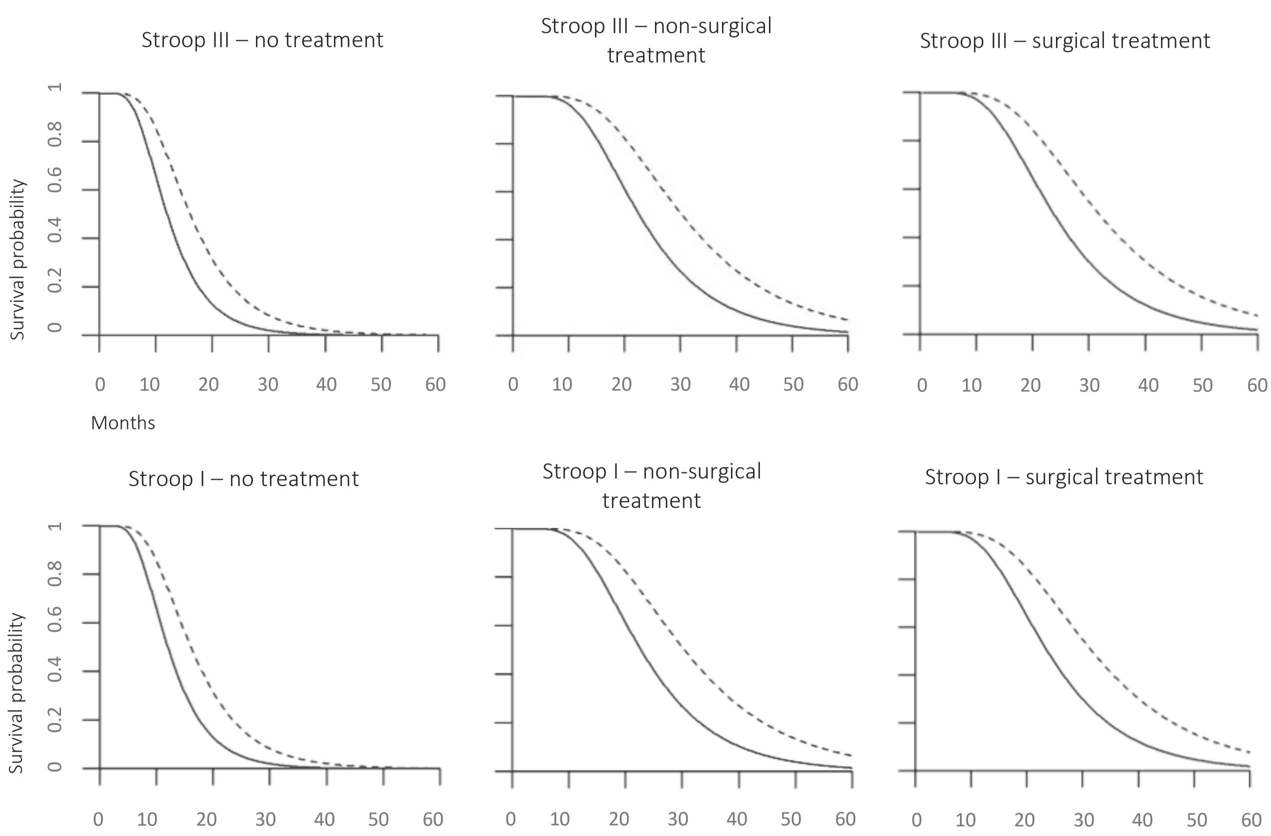

Figure. 2 Multivariate survival probabilities (y-axis) over time (in months, x-axis). Plots indicate impairment status on Stroop III (upper row) and Stroop I (lower row), under different *salvage* treatments. The dotted line (---) indicates non-impaired performance, the solid line (---) indicates impaired performance.

DISCUSSION

This study investigated to what extent cognitive performance three months after surgical resection was related to survival time in patients with GBM. We assessed the predictive value of cognition with AFT models while controlling for significant clinical prognostic factors (KPS, pre-surgical tumor volume, and salvage therapy) and covariates. Eighty-seven percent of patients showed impairment on at least one test, while 33% showed impairment on at least half of the tests. In line with available literature, we found that impairment on a test of executive functioning[17,19] (Stroop test III) independently predicted worse survival. We found a similar effect of processing speed (Stroop test I) impairment. Specifically, estimated median survival time was 26% shorter for patients with impairment on Stroop III compared to those without, and 23% shorter for patients with impairment on Stroop I compared to those without, translating into decreases of at least 4.0 and 3.6 months respectively in patients of good postoperative functional status (KPS 90-100), depending on salvage treatment. The continuous performance scores (Z-scores) did not reach the adjusted significance level, indicating that the prognostic bearing of cognition was limited to performances beyond a clinical threshold.

Taking into account previous reporting that patients with stable disease tend to show stable cognitive performance during early adjuvant treatment[27] and that dysfunction arising before 6-month follow up appears related to poorer survival outcome,[28] our results suggest that specific cognitive impairments during chemo-radiation reflect a worse prognostic outlook rather than an early treatment effect (otherwise due to e.g., acute encephalopathy[29,30] or treatment-induced fatigue[31]).

6

Notably, we found a relationship between cognitive impairment three months after surgery and salvage treatment, but they both exhibited independent associations with survival time. Treatment decisions are partly based on the patient's functional performance,[3] which itself is associated with cognition,[5] and clinicians might favor more radical treatment in patients with good cognitive status.[9] Incorporating information about salvage treatment in studies involving cognition and survival outcome is therefore warranted. We note that the prognostic bearings of salvage treatment as well as postsurgical KPS appear larger than that of postsurgical cognitive impairment. Nevertheless, cognitive measures acquired in addition to routine clinical follow up may facilitate early refinement of prognosis. Submitting vulnerable patients to exhaustive assessment for this purpose may not be not necessary, as performance on a limited range of tests, those assessing executive functioning in particular,[9] appear relevant.

Executive functioning encompasses and relies on various functions. Part III of the Stroop test measures executive control ability; making decisions on relevant information among distracting cues. As it engages multiple functions such as top-down attention, response selection, inhibition and evaluation, executive control recruits a distributed network involving the dorsolateral prefrontal cortex and anterior cingulate cortex.[32] Stroop I does not involve executive control, as it mainly reflects the speed at which subjects identify that a target is present (simple processing speed). However, slowed processing speed contributes to executive functioning deficits[33] and decreased processing speed together with memory and executive dysfunction has been suggested as a marker for more advanced disease.[34] The Trail Making Test part B, a test that has been shown to carry particular value in predicting survival,[11,17] also puts a demand on executive function in addition to mental speed.[35,36]

We did not find significant predictive roles for other tests that strongly depend on information processing speed, such as the Symbol Digit Coding (SDC) test. This might be attributable to the requirements of the test in CNS VS, where the subject presses different numbers on the keyboard based on the item. This involves computer familiarity and visuospatial scanning of the keyboard. Stroop I and III require the same simple motor response (pressing the space bar) to targets presented in the middle of the screen, which limits those factors. From our results, it does remain unclear whether processing speed underlay the prognostic effect of both Stroop tests, or if executive control exhibited a unique influence. Adopting different tests with varying speed and executive components might help to explore distinct contributions.

We acknowledge other limitations in this study that could also be addressed in future research. Firstly, we used cognitive status and KPS at one time-point instead of change therein. As a result, we cannot infer whether poor cognitive (and functional) performance reflected aggressive deterioration after surgery or a poor status that was already present. Future investigations might therefore include a short-term repeated measure of KPS and a cognitive classification that creates subgroups of patients that go from unimpaired pre-operative to impaired post-operative performance, indicating fast cognitive deterioration, and those who show impaired pre- and post-surgical status, indicating stable problematic functioning. Due to restrictions in sample size (valid T0 NPA and/or T0 KPS were not available for all patients), we were unable to perform these analyses in the current sample. In addition, we did not adopt IDH1 mutation status in our analyses, as it was available for only 66 patients. IDH1 mutation status is a major factor in distinguishing GBM subtypes[37] and predicting clinical outcome,[38] but has also been related to cognition.[39] The high proportion of wild type tumors in the available subsample was in line with data presented in the 2016 WHO Classification.[40] Still, we cannot conclude that our results are directly applicable to the small proportion of IHD1 mutated glioblastoma. Finally, conducting NPA three months after surgery coupled with regular care appointments has benefits from a logistical standpoint and allows for major stress from diagnosis and surgical intervention to subside. We have, however, observed in our study that this is a subgroup of patients who are clinically able and also willing return at this time.

Survival outcomes of patients with brain tumors in relation to cognition have primarily been reported using the hazard function, summarizing a predictor's effect in terms of rates of death in different groups. Models based on the survival curve, such as AFT,[21] may be more useful if a predictor is thought to convey a delay in the event occurring rather than an effect on the event itself occurring, and its derivative (Time Ratio) is arguable more clinically interpretable.[41] The AFT model as used here therefore appears to be an appropriate alternative to the commonly used Proportional Hazards model.

CONCLUSION

In conclusion, patients with GBM who displayed impairment on tests of executive functioning (Stroop III) and processing speed (Stroop I) three months after surgical resection had significantly reduced survival time (26% and 23% shorter respectively) compared to patients who did not show impairment. As KPS remains a principal clinical prognostic factor at the three-month time-point, targeted assessment of cognitive status incorporated as part of clinical follow-up care might allow for early refinement of disease monitoring. Further exploration of the prognostic value of different (speeded) measures of executive functioning and use of AFT models are recommended.

REFERENCES

1. Chambless LB, Kistka HM, Parker SL, et al. The relative value of postoperative versus preoperative Karnofsky Performance Scale scores as a predictor of survival after surgical resection of glioblastoma multiforme. *J Neurooncol.* 2015;121(2):359-364.
2. Li J, Wang M, Won M, et al. Validation and simplification of the Radiation Therapy Oncology Group Recursive Partitioning Analysis classification for glioblastoma. *Int J Radiat Oncol Biol Phys.* 2011;81(3):623-630.
3. Stark AM, Stepper W, Mehdorn HM. Outcome evaluation in glioblastoma patients using different ranking scores: KPS, GOS, mRS and MRC. *Eur J Cancer Care (Engl).* 2010;19(1):39-44.
4. Hutchinson TA, Boyd NF, Feinstein AR, et al. Scientific problems in clinical scales, as demonstrated in the Karnofsky index of performance status. *J Chron Dis*. 1979;32(9-10):661-666.
5. Noll KR, Bradshaw ME, Wefel JS, et al. Neurocognitive functioning is associated with functional independence in newly diagnosed patients with temporal lobe glioma. *Neurooncol Pract*. 2017;5(3):184-193.
6. Gately L, Collins A, Murphy M, et al. Age alone is not a predictor for survival in glioblastoma. (2016) *J Neurooncol*. 129(3):479-485. 7.
7. Lamborn KR, Chang SM, Prados MD. Prognostic factors for survival of patients with glioblastoma: recursive partitioning analysis. *Neuro Oncol. 2004*; 6(3):227-235.
8. Asher A, Fu JB, Bailey C, et al. Fatigue among patients with brain tumors. *CNS Oncol*. 2016;5(2):91-100.
9. Johnson DR, Wefel JS. Relationship between cognitive function and prognosis in glioblastoma. *CNS Oncol.* 2013;2(2):195-201.
10. Brown PD, Buckner JC, O'Fallon JR, et al Importance of baseline mini-mental state examination as a prognostic factor for patients with low-grade glioma. *Int J Radiat Oncol Biol Phys*. 2004;59(1):117-125.
11. Lee S-T, Park C-K, Kim JW, et al Early cognitive function tests predict early progression in glioblastoma. *Neurooncol Pract.* 2015;2(3):137-143.
12. Taphoorn MJ, Klein M.Cognitive deficits in adult patients with brain tumours. *Lancet Neurol.* 2004;3:159-168.
13. Ali FS, Hussain MR, Gutiérrez C, et al. Cognitive disability in adult patients with brain tumors. *Cancer Treat Rev. 2018*;65:33-40.
14. Habets EJ, Kloet A, Walchenbach R, et al. Tumour and surgery effects on cognitive functioning in high grade glioma patients. *Acta Neurochir (Wien).* 2014;156(8):1451-1459.
15. van Loenen IS, Rijnen SJM, Bruijn J, et al. Group Changes in Cognitive Performance After Surgery Mask Changes in Individual Patients with Glioblastoma. *World Neurosurg.* 2016;117:e172-e79.

16 Gorlia T, van den Bent MJ, Hegi ME, et al. Nomograms for predicting survival of patients with newly diagnosed glioblastoma: prognostic factor analysis of EORTC and NCIC trial 26981-22981/CE.3. *Lancet Oncol.* 2008;9(1):29-38.

17. Johnson DR, Sawyer AM, Meyers CA, et al. Early measures of cognitive function predict survival in patients with newly diagnosed glioblastoma. *Neuro-Oncol.* 2012;14(6):808-816.

18. Klein M, Postma TJ, Taphoorn MJ, et al. The prognostic value of cognitive functioning in the survival of patients with high-grade glioma. *Neurology.* 2003;61(12):1796-8.

19. Noll KR, Sullaway CM, Wefel JS. Depressive symptoms and executive function in relation to survival in patients with glioblastoma. *J Neurooncol.* 2019;142(1):183-191.

20. Tanzilli A, Pace A, Fabi A, et al. Neurocognitive evaluation in older adult patients affected by glioma. *J Geriatr Oncol*. 2019 (epub) https://doi.org/10.1016/j.jgo.2019.06.015

21. Wei LJ. The accelerated failure time model: A useful alternative to the cox regression model in survival analysis. *Stat Med.* 1992;11(14-15):1871-1879.

22. Butterbrod E, Bruijn J, Braaksma MM, et al. Predicting disease progression in high-grade glioma with neuropsychological parameters: the value of personalized longitudinal assessment. *J Neurooncol*. 2019;144(3):511-518.

23. Gualtieri CT, Johnson LG. Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs. *Arch Clin Neuropsychol.* 2006;21(7):623-643.

24. Rijnen SJM, Meskal I, Emons WHM, et al. Evaluation of normative data of a widely used computerized neuropsychological battery: applicability and effects of sociodemographic variables in a dutch sample. *Assessment*. 2017 (epub) https://doi.org/10.1177/1073191117727346

25. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: a practical and powerful approach to multiple testing. *J R Stat Soc B.* 1995;57(1):289-300.

26. Therneau T. A package for survival analysis in S. Version 2.44-1.1. https://CRAN.Rproject.org/package=survival.

27. Hilverda K, Bosma I, Heimans JJ, et al. Cognitive functioning in glioblastoma patients during radiotherapy and temozolomide treatment: initial findings. *J Neurooncol.* 2010;97(1):89-94.

28. Brown PD, Jensen AW, Felten SJ, et al. Detrimental effects of tumor progression on cognitive function of patients with high-grade glioma. *J Clin Oncol.* 2006;24(34):5427-5433.

29. Wefel JS, Kayl AE, Meyers CA. Neuropsychological dysfunction associated with cancer and cancer therapies: a conceptual review of an emerging target. *Br J Cancer.* 2004; 90(9):1691-96.

30. Wu PH, Coultrap S, Pinnix C, et al.Radiation induces acute alterations in neuronal function. *PLOS ONE*. 2012;;7(5):e37677.

31. Butler JM, Rapp SR, Shaw EG.Managing the cognitive effects of brain tumor radiation therapy. *Curr Treat Options Oncol.* 2006;7(6):517-523.

32. Banich MT. Executive function: the search for an integrated account. *Curr Dir Psychol Sci.* 2009;18(2):89-94.

33. Leavitt VM, Wylie G, Krch D, et al. Does slowed processing speed account for executive deficits in Multiple sclerosis? Evidence from neuropsychological performance and structural neuroimaging. *Rehab Psychol.* 2014;59(4):422-8.

34. Giovagnoli AR.Investigation of cognitive impairments in people with brain tumors. *J Neurooncol.* 2012; 108(2):277-83.

35. MacPherson SE, Cox SR, Dickie DA, et al. Processing speed and the relationship between Trail Making Test-B performance, cortical thinning and white matter microstructure in older adults. *Cortex.* 2017;95:92-103.

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36. Tombaugh TN.Trail Making Test A and B: Normative data stratified by age and education. *Arch Clin Neuropsychol*. 2004;19(2):203-14.

37. Molinaro AM, Taylor JW, Wiencke JK, et al. Genetic and molecular epidemiology of adult diffuse

glioma. *Nat Rev Neurol.* 2019;15(7):405-417.

38. Hartmann C, Hentschel B, Wick W, et al. Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas. *Acta Neuropathol.* 2010;120(6):707-718.

39. van Kessel E, Emons MAC, Wajer IH, et al. Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a retrospective cohort study prior to antitumor treatment. *Neurooncol Pract.* 2019; 6(6):463-39.

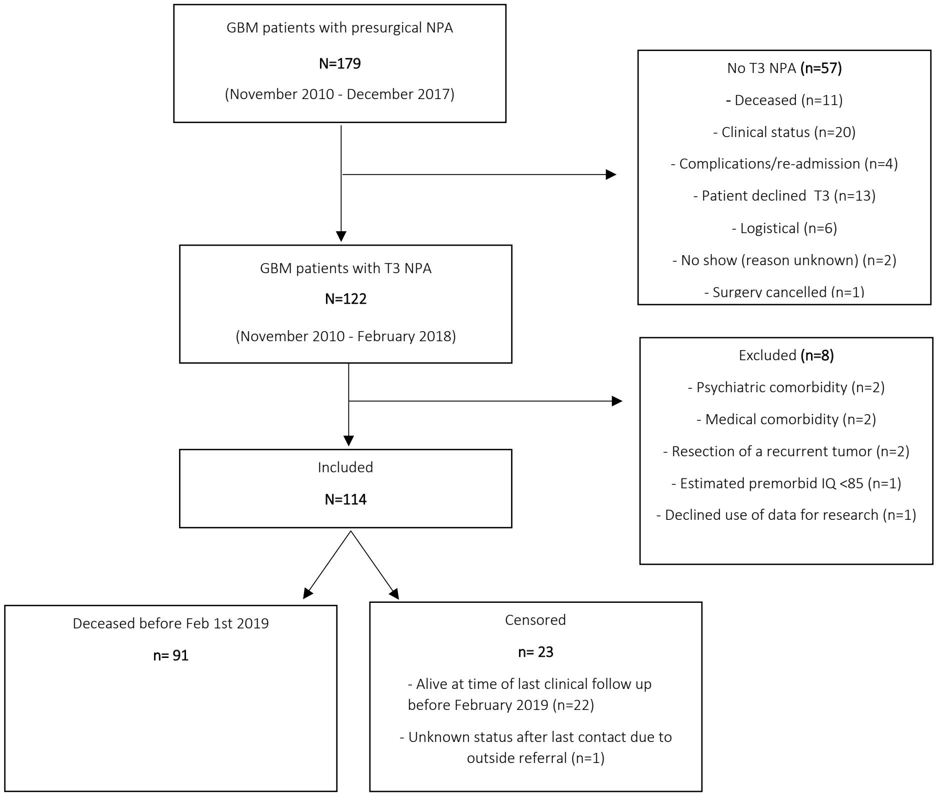
40. Louis DN, Perry AP, Reifenberger, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol.* 2016;131(803-820).

41. Kay R, Kinnersley N. On the use of the Accelerated Failure Time model as an alternative to the Proportional Hazards model in the treatment of time to event data: a case study in influenza. *Ther Innov Regul Sci.* 2002;36(3):571-579.

SUPPLEMENTARY MATERIALS

Supplementary table 1 Description of used CNS VS tests

Test	Content	Score computation
CNS VS Verbal Memory (VEM) Test	Fifteen words are presented, one at a time. Subject subsequently identifies presented words among new words by pressing the space bar (immediate and delayed recall).	Total items correct (hits and passes)
CNS VS Visual Memory (VIM) Test	Fifteen abstract images are presented, one at a time. Subject subsequently identifies presented images among new images (immediate and delayed recall).	Total items correct (hits and passes)
CNS VS Finger Tapping Test (FTT): *Motor speed*	Subject presses the space bar as quickly as possible for 10 seconds with the index finger (three trials for the left and the right hand).	Taps right average + taps left average
CNS VS Symbol Digit Coding (SDC) Test: *Psychomotor speed*	Symbols and corresponding numbers are displayed in the upper part of the screen. Subject matches symbols with correct numbers in a grid on the lower part of the screen for two minutes.	Correct responses – incorrect responses
CNS VS Stroop Test part I (Stroop I): *Simple reaction time*	Part 1: subject presses space bar when a word is presented on the screen. All words describe colors.	Average reaction time
CNS VS Stroop Test part III (Stroop III): *Inhibitory control*	Part 3: subject presses space bar if the color of the word does not match the meaning of the word (incongruent trials, e.g., the word “green” is presented with a red font).	Average reaction time correct items
CNS VS Shifting Attention Test (SAT): *Cognitive flexibility*	Subject matches geometric objects by either shape or color to one of two figures in the lower part of the screen for two minutes, using the left and right shift keys. The assignment and figures differ per trial.	Correct responses – Errors
CNS VS Continuous Performance Test (CPT): *Vigilance*	Capital letters are presented on the screen, one at a time. Subject responds to only target letter “B” by pressing the space bar (total test time 5 minutes, uninterrupted).	Average reaction time of responses to target letter



Supplementary figure 1. Overview of patient inclusion

CHAPTER 7

Predicting disease progression in high-grade glioma with neuropsychological parameters: the value of personalized longitudinal assessment

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ABSTRACT

Purpose Progressive disease in patients with high-grade glioma may be reflected in cognitive decline. However, the cognitive functions most sensitive to progression may differ between patients. We investigated whether decline on a personalized selection of tests predicted progressive disease according to RANO criteria in high-grade glioma patients.

Methods Starting one day before surgery, patients underwent neuropsychological assessment every three months during standard treatment and clinical follow-up. We first made a personalized selection of three tests that showed the highest Reliable Change Index (RCI) values, i.e., most positive change, at the first post-surgical assessment for each patient. In subsequent follow up, a decline of RCI≤−1 on at least two of the three tests in the selection was considered cognitive decline. We performed a discrete Cox proportional hazards model including a time-dependent coefficient cognitive decline (vs. stability) and covariate age to predict progressive disease.

Results Twenty five patients were included. Cognitive decline on the personalized test selection preceded or had occurred by the time progression was established in 9/15 patients with RANO confirmed progressive disease (60%). Decline was absent in 8/10 patients (80%) with stable disease during participation. The independent hazard ratio for progression in case of cognitive decline was 5.05 ($p <$ 0.01) compared to stable performance.

Conclusions Using only three patient-specific neuropsychological tests, we found a fivefold increased chance of disease progression in case of cognitive decline as compared to stable performance. Brief, patient-tailored cognitive assessment may be a noninvasive addition to disease monitoring without overburdening patients and clinical care.

INTRODUCTION

Identification of reliable prognostic indicators for disease progression and overall survival is a principal aim in care for patients with high-grade gliomas (HGG), for treatment planning and to inform patients. Age and performance status (PS) are generally considered the major prognostic factors from a clinical perspective.[1–3] These characteristics, however, may be interrelated with or confounded by other factors, such as therapeutic strategy or varying disease symptoms,[1, 4] that are not always accounted for. Interest in the prognostic value of cognitive functioning in the clinical management of glioma patients is growing. [1, 5–9] Cognitive functioning depends on neuronal synchrony across brain regions.[10] Invasive growth, reactive changes in peritumoral tissue and increased intracranial pressure may all disrupt network functioning needed for cognitive performance.[11]

Cognitive status before surgery or oncological treatment has been reported as a predictor of (progression-free) survival time[7] independent of age and Karnofsky PS (KPS),[9] as well as within RPA-RTOG classes.[12] Furthermore, Meyers[8] reported that performance decline over time on one of nine cognitive tests preceded radiological evidence of progressive disease (PD) in HGG in 85% of cases and by a median of 4 to 7 weeks. In a heterogeneous sample of patients with brain tumors, Armstrong and colleagues[5] showed that a decline of one standard deviation (SD) on the standardized mean of three to five tests per patient selected based on tumor location, was accompanied by a fivefold increase in chance of PD.

Cognitive deterioration over time might thus provide information about tumor activity during the course of the disease.[5, 8, 13, 14] A targeted test selection, e.g., tumor location-based,[5] may increase efficiency of assessment. However, dysfunction of specific cognitive domains may not be reliably determined by location alone[15, 16] as tumors affect cerebral functioning outside their location.[17]

In this study, we argue that disease-related cognitive dysfunction in HGG, and individual differences therein, may also be detected by considering the manner in which a patient's performance changes early after tumor resection. We hypothesize that the functions that show the largest recovery shortly after surgery are the ones that suffered the largest burden from tumor-related edema and mass effect, and that these same functions may deteriorate first amid recurrent disease activity. In a sample of newly diagnosed HGG, we constructed a personalized test selection for each patient, based on a subset of three neuropsychological tests that demonstrated most improvement within three months after resection. We subsequently investigated whether deterioration on this selection coincided with, and predicted PD.

MATERIALS AND METHODS

Patients

Patients undergoing resection at the Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands, between August 2015 and September 2017 for histopathologically confirmed WHO grade III anaplastic astrocytoma (AA) or WHO grade IV glioblastoma (GBM) were included. Patients received clinical follow up either at Elisabeth-TweeSteden Hospital or Catharina Hospital, Eindhoven, the Netherlands. Exclusion criteria were age <18, presence of progressive neurological disease, psychiatric or acute neurological disorder within the past 2 years, previous intracranial surgery, reduced testability (e.g. lack of proficiency in Dutch, estimated IQ<85). All participants provided written informed consent.

Study procedure and design

At the neurosurgery department of Elisabeth-TweeSteden Hospital, patients with brain tumors undergo neuropsychological assessment (NPA) as part of clinical care 1 day before (T0) and 3 months after (T3) neurosurgical treatment. Around T3, patients were asked to participate in this prospective longitudinal study by a neuro-oncology nurse practitioner, and underwent three monthly NPA and MRI, for up to 24 months after surgery (T24; 9 NPA's in total) or until confirmed progressive disease (PD) at their clinical follow-up site. NPA and MRI were performed on the same day, but NPA was always done before the patient was informed of the results of the MRI. Approval for the study was given by Medical Ethics Committee Brabant (File No. NL41351.008.12).

Measures

Sociodemographic and clinical measures

Sociodemographic information was gathered through semi-structured interview at T0. Clinical information (tumor characteristics, extent of resection, KPS, medication, adjuvant treatment) was retrieved from electronic charts. Pre-surgical tumor volumes were determined through semi-automatic segmentation using BrainLab Elements[18] software on T1-post contrast enhanced series.

Neuropsychological assessment

The Dutch translation of the CNS Vital Signs (CNS VS) computerized test battery consists of seven tasks based on conventional paper-and-pencil tests.[19] Completion using the local software application on a notebook computer took 30–40 min. Two additional paper-and-pencil tasks were administered: Digit Span task[20] and a Letter Fluency task.[21]

An overview of task content and score computation is provided in the supplementary Table. Trained test administrators conducted assessments.

MRI-cerebrum and time until PD

Evaluations of the three monthly MRI scans were conducted by a trained neurologist (MB) under supervision of a senior neurologist (CT), both unaware of patients' cognitive status. The baseline for comparison follow up MRI scans (at T3, T6, etc.) was the first post-operative scan (≤48 h after surgery). We adopted the response assessment criteria for HGG by the RANO Working Group[22] for disease status evaluation: (1) ≥25% increase of the product of the Journal of Neuro-Oncology (2019) 144:511–518 513 1 3 maximum diameters of contrast-enhancing lesions (2) significant increase of lesions in T2-weighted/ FLAIR series (3) presence of new contrast-enhancing lesions outside radiation field (4) significant clinical deterioration not attributable to medication or comorbid conditions, or (5) clear progression of a non-measurable lesion.

Cognitive change as a personalized predictor

Reliable change

Regression-based Reliable Change Indices (RCI), aimed at determining whether change between assessments in individual patients reflected relevant change, controlling for confounding factors related to repeated testing (e.g. flawed test–retest reliability, practice effects),[23, 24] were computed for each of the 10 test scores. A positive RCI value indicates improvement, a negative RCI value indicates decline. RCI's were based on repeated testing data of healthy Dutch individuals from Rijnen[24] (CNS VS), Schmand[21] (Letter Fluency), and an ongoing study in the ETH (Digit Span test); CAR study A, ClinicalTrials.gov reference nr. NCT02953756.

Personalized selection and criterion for cognitive decline (CD)

For each patient, the three tests with the highest RCIs between T0 and T3 were selected. We opted to select three tests in accordance with previous similar studies,[5, 8] and with the goal of a small selection of tests for potential future clinical purposes. All follow-up RCI's were calculated using T3 NPA as baseline (T6–T3, T9–T3, etc.). CD was defined as RCI ≤ −1.00, reflecting a standardized difference score of −1, on at least two of the three selected tests at any follow up interval.

Statistical analyses

Using the Survival package in Rstudio, a discrete Cox proportional hazards model with two covariates was performed (α=0.05): a dichotomous time-dependent covariate (CD vs. stable performance) and age at time of surgery. Cases who dropped out before PD, completed follow up (T24) progression-free, or showed stable disease at the end of the study (August 2018), were censored. Median time to PD and to CD were computed.

Z-scores, corrected for age, sex and educational level based on a healthy control sample[25] were computed to investigate whether patients had cognitive impairment before surgery ($Z \leq -1.5$). Group-level characteristics of patients with PD, without PD, with CD, and without CD were computed (no statistical comparisons due to sample sizes).

RESULTS

Patients

Thirty-five of 70 (50%) patients eligible for participation were included in the study. Unwillingness, anticipated intensity of repeated NPA, and follow-up care in a non-participating center were reasons for declining participation. Ten out of 35 patients were excluded from analyses, because of invalid or incomplete T0 NPA (n=6), or absent T6 data (consent withdrawal; n=3, referral to non-participating treatment center; n=1). Analyses showed no differences in age, tumor volume, extent of resection or pre-operative KPS between excluded patients and the final sample. The final sample comprised four AA and 21 GBM.

Mean age at time of surgery was 53 ± 14 years. See Table 1 for an overview of sample characteristics and Table 2 for the personalized test selection per patient. All patients started adjuvant chemoradiation according to protocol.[26] Twenty-one patients completed treatment as planned during study participation. Temozolomide monotherapy was discontinued in four patients, either on patient's request (n=1, around T6), because of PD during (n = 2, around T6) or due to treatment-related toxicity (n=1, between T6 and T9)

Table 1. Sample characteristics

Characteristic	N=25
Male *n* (%)	17 (68%)
Age at time of surgery (M±SD, range)	53±14, 19-76
Educational level†	
Low *n* (%)	3 (12%)
Middle *n* (%)	12 (48%)
High *n* (%)	10 (40%)
Diagnosis	
Glioblastoma	21 (84%)
Anaplastic astrocytoma	4 (16%)
Tumor volume (cm^3), median (range)	36.8 (4.4–161.5)
KPS before surgery, mode (range)	90, 80-100
Tumor lateralization *n* (%)	
Right	15 (60%)
Left	10 (40%)
Tumor location *n* (%)	
Frontal	6 (24%)
Fronto-parietal	1 (4%)
Parietal	3 (12%)
Parieto-temporal	2 (8%)
Parieto-occipital	4 (16%)
Temporal	3 (12%)
Occipital	6 (24%)
Corticosteroids before surgery	17 (68%)
Anti-epileptics before surgery	8 (32%)
Macroscopic extent of resection	
Gross total resection (>90%)	17 (68%)
Gross subtotal resection (<90%)	8 (31%)

†Classified according to Verhage education coding system[26]

Table 2. Cognitive parameters and tumor location per patient

Diagnosis	Age	Location	Hemisphere	Selected tests	Impairment on selected tests at T0[a]	PD during follow up
GBM	18-20	Frontal	left	SAT, LF, SDC	3/3	No[§]
GBM	60-70	Parieto-occipital	right	SAT, VEM, SDC	2/3	Yes
AA	30-40	Frontal	left	DSFW, LF, SAT	1/3	No[§]
GBM	60-70	Occipital	left	VIM, DSB, DSF	0/3	Yes
GBM	50-60	Occipital	right	SDC, CPT, FTT	2/3	Yes
GBM	50-60	Fronto-parietal	right	SAT, VIM, VEM	1/3	Yes
GBM	40-50	Frontal	right	SAT, CPT, FTT	2/3	Yes
GBM	60-70	Parietal	right	CPT, SAT, VEM	3/3	Yes
GBM	60-70	Occipital	right	VIM, SAT, VEM	3/3	Yes
GBM	40-50	Frontal	left	FTT, CPT, SAT	0/3	Yes
GBM	50-60	Parieto-occipital	left	SAT, CPT, SDC	1/3	No[‡]
GBM	50-60	Parietal	left	SAT, VIM, FTT	3/3	Yes
GBM	50-60	Parieto-occipital	right	FTT, CPT, SDC	3/3	No[‡]
AA	30-40	Frontal	right	VIM, VEM, LF	0/3	No[§]
GBM	60-70	Temporo-parietal	left	FTT, SAT, Stroop	0/3	Yes
GBM	70-80	Parietal	right	FTT, SAT, Stroop	2/3	Yes
GBM	50-60	Frontal	right	FTT, VIM, DSF	0/3	Yes
GBM	50-60	Occipital	right	VEM, VIM, LF	2/3	Yes
GBM	50-60	Temporo-parietal	left	FTT, VEM, Stroop	0/3	Yes
GBM	30-40	Occipital	right	FTT, DSF, SDC	2/3	No[‡]
GBM	70-80	Temporal	right	Stroop, SAT, VIM	0/3	Yes
GBM	50-60	Occipital	right	VIM, Stroop, FTT	1/3	No[†]
GBM	50-60	Mesiotemporal	left	FTT, LF, SDC	3/3	No[†]
AA	50-60	Temporal	right	SAT, SDC, DSB	3/3	No[†]
AA	20-30	Parieto-occipital	left	FTT, VEM, DSB	2/3	No[†]

[†]active participation at end of study, [‡]Dropout before PD, [§]Completion of T24 without PD

Cognitive change and progressive disease

In 23 out of 25 patients, all three selected tests with the highest RCI from T0 to T3 were positive scores (>0), indicating improvement after surgery. In two patients, the selection also contained tests with negative values (highest RCI's were 0.62, 0.23, and −0.25 in one patient, 1.76, −0.18, and −0.20 in another patient).

Fifteen out of 25 patients (60% of the sample) showed PD according to RANO during follow up (see Table 3 for evaluations of PD). Eleven out of 25 showed CD during follow up. Within the "PD group", the median time-point to PD was T9, while within the "CD group", the median time-point to CD was T6. CD preceded (n=4) or was present at time of (n=5) PD in nine out of 15 patients with PD. See Fig. 1 for a visualization of individual follow-up periods and the timing of CD relative to PD. Five of the six patients who showed stable cognitive performance according to our criterion, despite PD, showed RCI≤−1 on one of their selected tests at time of PD, while showing no RCI≤−1 on their unselected tests.

In 10 of 25 patients (40%), PD did not occur during study participation. Eight out ten (80%) were stable performers throughout follow up (median follow up time-point T12, range T6–T24). Two patients showing CD despite stable disease did so at T6 and T9 respectively.

Table 3 shows descriptive characteristics of the four groups (no statistical comparisons). The group demonstrating both CD and PD was the only group in which KPS below 90 was observed at time of final NPA. AED use was high among these patients compared to the other groups, but the majority (four out of six) used medication because of a pre-surgical insult. The other two started AED therapy due to a seizure during follow up (both in the interval prior to PD). The group with stable disease and stable cognitive performance appeared relatively young and to comprise fewer males compared to the other groups.

Cox proportional hazards model

The Cox proportional hazards model showed a hazard ratio (HR) for PD of 5.05; 95% CI 1.50–17.02, $p < 0.01$ (model $\chi 2$ [1] = 13.6, $p < 0.01$, c-index = 0.80), suggesting a 405% increase in chance of RANO-confirmed PD if patients met the criterion of CD compared to stable cognitive performance, independent of age. Age itself was not a significant predictor (HR=1.04, $p > 0.1$) of PD.

7

Table 3. Descriptive characteristics and RANO[22] evaluations grouped by disease status and cognitive status on personalized test selections. Percentages are calculated within each group.

Progressive disease (n=15)	**Decline on tests n=9**	**Stable on tests n=6**
Age before surgery	60.0±7.6	58.3±10.7
Low education	0 (0%)	1 (16.7%)
High education	4 (44.4%)	3 (50%)
Male	7 (77.8%)	5 (83.3%)
Impairment on ≥1 selected test at T0	5 (55.6%)	5 (83.3%)
Tumor in left hemisphere	4 (44.4%)	1 (16,7%)
Macroscopic total resection	6 (66.7%)	3 (50%)
Time to CD (Median)	T6	n/a
Time to PD (Median)	T6	T12
KPS <90 at time of PD	5 (55.6%)	0 (0%)
AEDs at time of PD (%, n at T3)	6 (66.7%, 5)	1 (16.7%)
Corticosteroids at time of PD	2 (22.2%)	0 (0%)
RANO evaluation		
New contrast-enhancing lesion outside radiation field	0 (0%)	1 (16.7%)†
Increase ≥25% in the sum of the products of perpendicular diameters	5 (55.6%)	3 (50%)
Clinical deterioration not attributable to medication or comorbidity (≥12 weeks post-chemoradiation)	1 (11.1%)	0 (0%)
Significant increase in T2/FLAIR non-enhancing lesion	0 (0%)	0 (0%)
Clear progression of a non-measurable lesion	3 (33.3%)	2 (33.3%)
Stable disease (n=10)	**Decline on tests n=2**	**Stable on tests n=8**
Age before surgery	55.5±3.54	40.3±15.6
Low education	0 (0%)	2 (25%)
High education	1 (50%)	4 (50%)
Male	2 (100%)	3 (37.5%)
Impairment on ≥1 selected test at T0	2 (100%)	7 (87.5%)
Tumor in left hemisphere	1 (50%)	4 (50%)
Macroscopic total resection	2 (100%)	6 (75%)
Time to CD (Median)	T6	n/a
Time to PD (Median)	n/a	n/a
KPS <90 at time of censoring	0 (0%)	0 (0%)
AEDs at time of censoring (%, n at T3)	0 (0%, 0)	2 (25%, 2)
Corticosteroids at time of censoring	0 (0%)	0 (0%)

† Only case of non-local tumor recurrence

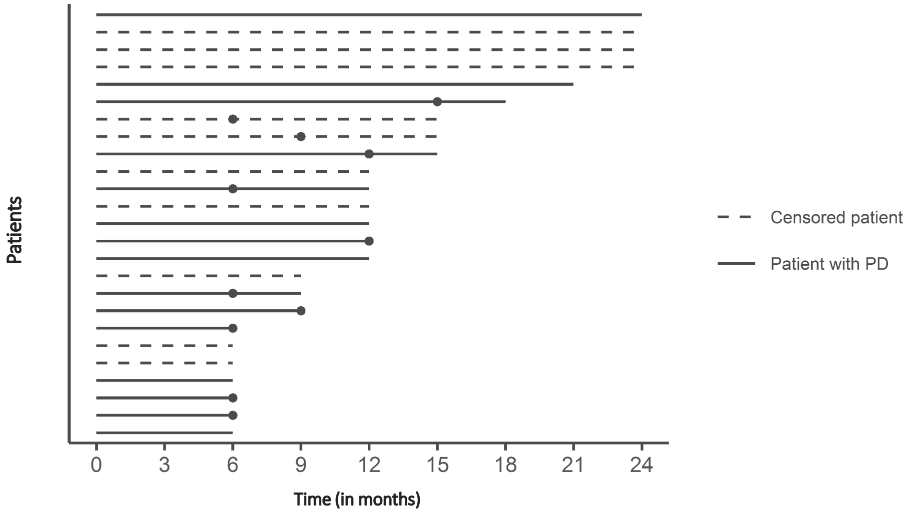


Figure 1 Follow up duration per patient and time of CD (●) Lines stop at time of RANO PD (bold line) or end of participation (dotted line; censoring).

DISCUSSION

This study investigated whether post-surgical cognitive decline (CD) on a personalized selection of three neuropsychological tests concurred with and predicted progressive disease (PD) according to RANO[22] in 25 patients with GBM or AA.

Decline in cognitive performance—deterioration of at least one RCI point on at least two of the three selected tests—concurred with, or manifested one or two interval(s) before, RANO-confirmed PD in nine out of 15 (60%) of recurrences. Of the six patients with PD who did not meet our criterion for CD, five showed RCI≤ −1on one of their selected tests, but no such decline on their unselected tests. Further consistent with our hypothesis and previous reporting,[27] eight out of 10 patients with stable disease remained cognitively stable throughout participation. The predictive model showed a 405% increase in chance for PD (HR=5.05) in case of CD, independent of age.

Our findings support existing reports of (change in) cognitive functioning as a clinical marker of disease activity in patients with brain tumors.[5, 8, 13, 28] Gradual, widespread impairment of network functioning over time may underlie the sensitivity of cognitive performance to disease progression. Using a uniform test selection in patients with recurrent HGG, Meyers and colleagues[8] reported a higher proportion of patients showing CD (48/56 patients, CD was defined as RCI≤−1.645 on one of nine tests) before, or at time of, PD compared to our study. It could be that CD emerges sooner in patients with progression of already recurred HGG. Still, the described criterion for decline was based on a more stringent cutoff, but for only one test, and time between CD and actual PD seemed to vary considerably among patients. Their reported prediction model (requiring decline on one of three uniform tests) yielded a HR for PD of 2.0 in case of CD.

The hazard ratio of CD (one standard deviation in mean performance) on a tumor location-based selection of three to five tests found by Armstrong[5] in a sample of 34 patients with glial and non-glial tumors, of which 11 demonstrated recurrence, was comparable to the one we found. As stated, reliable inferences about cognitive (dys-)function may not be based on tumor location alone.[15] In our sample of mainly GBMs, we did not observe a one-to-one relationship between tumor location and the personalized selection of tests, e.g., Letter Fluency and Shifting Attention tests were selected in patients with occipital tumors. The relative value of selection approaches (uniform, location-specific, personalized) within the context of prediction of PD may be compared in one larger sample in the future.

The absence of a gold standard concerning the cut off for CD, irrespective of the selection approach, in settings where cognition is used as a predictive instead of an outcome measure also warrants further investigation. The used RCI is a suitable measure for change as it conveys a cautious estimation of decline. Selecting three tests per patient is in accordance with previous approaches[5,8] and preserves briefness required for repeated NPA in the HGG population. We must note that the widely adopted RANO criteria for HGG are based on current evidence[22] and will likely evolve in the future.

Cognitive performance can fluctuate over time due to factors (un-)related to disease activity, such as temporary corticosteroid use[29] or depressive symptoms.[30] It has however been suggested that the main cause of cognitive decline over time is the tumor itself.[13] Cognitive stability in eight out of 10 progression-free patients in this study also suggests that such factors did not disturb cognitive performance strongly (RCI's remained>−1) or in a personalized pattern. The group with both CD and PD did seem to comprise a relatively large proportion of patients using AED's, although in the majority of cases due to a pre-surgical insult. It was also the only group that comprised patients with KPS < 90 at time of final NPA/ PD. Clinical status may have interplayed with cognitive functioning around the time of PD. We were unable to adopt post-surgical decline in KPS or a combined cognition-KPS classification in the statistical model due to sample size, but analysis of hazard rates associated with CD irrespective of (K)PS decline could be a next step in future research.

Sample characteristics should be taken into account in interpreting our results. We note that our sample primarily comprised patients with GBM, and the majority of AA patients did not show PD. Moreover, 50% of patients who were invited to participate in this study declined participation, e.g., due to anticipated intensity of repeated NPA. Patients in good clinical condition at time of inclusion might therefore be overrepresented. Furthermore, only 12% of the included patients had low educational level. Different cognitive courses might exist between groups who differ on these variables.

Results from the personalized prediction model warrant further investigation to establish relevance in clinical practice. Personalized NPA may serve as a noninvasive method to complement decision making processes, such as timing of second-line therapy in case of unclear or seemingly limited tumor growth. Conducting targeted NPA between MRI scans may also allow for early detection of recurrent disease activity, e.g., in patients whose radiological evaluation is conducted over longer intervals due to other relatively favorable prognostic features.

CONCLUSION

In conclusion, our prediction model based on a personalized selection of three neuropsychological tests showed CD before or at time of PD in the majority of patients with HGG. Eighty percent of progression-free survivors showed stable cognitive performance. Patients demonstrating CD showed five times higher chance of PD compared to stable performers. Personalized, longitudinal NPA may provide a targeted and sensitive addition to monitoring of both cognitive and disease status without overburdening patients or care trajectories.

REFERENCES

1. Johnson DR, Wefel JS. Relationship between cognitive function and prognosis in glioblastoma. *CNS Oncol*. 2013;2:195-201.
2. Lamborn KR, Chang SM, Prados MD. Prognostic factors for survival of patients with glioblastoma: recursive partitioning analysis. *Neuro- Oncology*. 2004;6:227-235.
3. Weller M, Felsberg J, Hartmann C, Berger H, Steinbach JP, Schramm J, et al. Molecular predictors of progression-free and overall survival in patients with newly diagnosed glioblastoma: a prospective translational study of the German Glioma Network. *J Clin Oncol*. 2009;27:5743-5750.
4. Gately L, Collins A, Murphy M, Dowling A. Age alone is not a predictor for survival in glioblastoma. *J Neuro-Oncol.* 2016;129:479-485.
5. Armstrong CL, Goldstein B, Shera D, Ledakis GE, Tallent EM. The predictive value of longitudinal neuropsychologic assessment in the early detection of brain tumor recurrence. *Cancer*. 2003; 97:649-656.
6. Klein M, Postma T, Taphoorn M, Aaronson N, Vandertop W, Muller M, et al. The prognostic value of cognitive functioning in the survival of patients with high-grade glioma. *Neurology*. 2003; 61:1796-1798.
7. Lee S-T, Park C-K, Kim JW, Park M-J, Lee H, Lim J-A, et al. Early cognitive function tests predict early progression in glioblastoma. *Neurooncol Pract*. 2015;2:137-143.
8. Meyers CA, Hess KR. Multifaceted end points in brain tumor clinical trials: Cognitive deterioration precedes MRI progression. *Neuro-oncology.* 2003;5:89-95.
9. Meyers CA, Hess KR, Yung WA, Levin VA. Cognitive function as a predictor of survival in patients with recurrent malignant glioma. *J Clin Oncol*. 2000;18:646-650.
10. Uhlhaas PJ, Singer W.Neural Synchrony in Brain Disorders: Relevance for Cognitive Dysfunctions and Pathophysiology. *Neuron.* 2006;52:155-168.
11. Habets EJ, Kloet A, Walchenbach R, Vecht CJ, Klein M, Taphoorn MJ. Tumour and surgery effects on cognitive functioning in high-grade glioma patients. *Acta Neurochir*. 2014; 156:1451-1459.
12. Johnson DR, Sawyer AM, Meyers CA, O'neill BP, Wefel JS. Early measures of cognitive function predict survival in patients with newly diagnosed glioblastoma. *Neuro-oncology.* 2012; 14:808-816.
13. Brown PD, Jensen AW, Felten SJ, Ballman KV, Schaefer PL, Jaeckle KA, et al. Detrimental effects of tumor progression on cognitive function of patients with high-grade glioma. *J Clin Oncol.* 2006;24:5427-5433.
14. Bosma I, Vos MJ, Heimans JJ, Taphoorn MJ, Aaronson NK, Postma TJ, et al. The course of neurocognitive functioning in high-grade glioma patients. *Neuro-oncology*. 2007:9:53-62.
15. Anderson SW, Damasio H, Tranel D. Neuropsychological impairments associated with lesions caused by tumor or stroke. *Arch Neurol-Chicago*. 1990;47:397-405.
16. Carrera E, Tononi G. Diaschisis: past, present, future. *Brain*. 2014;137:2408-22.

17. Heimans JJ, Reijneveld JC. Factors affecting the cerebral network in brain tumor patients. *J Neurooncol.* 2012;108:231-237.

18. *BrainLab Elements*. Munich, Germany: BrainLab; 2018.

19. Gualtieri CT, Johnson LG. Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs. *Arch Clin Neuropsych*. 2006;21:623-643.

20. Wechsler D. WAIS-III administration and scoring manual. San Antonio: TX: The Psychological Corporation; 1997.

21. Schmand B, Groenink S, van den Dungen M. Letter fluency: Psychometric properties and Dutch normative data. *Tijdschr Gerontol Geriat*. 2008;39:64.

22. Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, et al. Updated response assessment criteria for high-grade gliomas: Response assessment in neuro-oncology working group. *J Clin Oncol*. 2010;28:1963-1972.

23. Maassen GH, Bossema E, Brand N Reliable change and practice effects: outcomes of various indices compared. *J Clin Exp Neuropsych*. 2009;31:339-352.

24. Rijnen SJM, van der Linden SD, Emons WHM, Sitskoorn MM, Gehring K. Test-retest reliability and practice effects of a computerized neuropsychological battery: A solution-oriented approach. *Psychol assessment.* 2018;30: 1652-1662.

25. Rijnen SJ, Meskal I, Emons WH, Campman CA, van der Linden SD, Gehring K, et al. Evaluation of normative data of a widely used computerized neuropsychological battery: Applicability and effects of sociodemographic variables in a Dutch sample. *Assessment.* 2017 (epub) doi: 10.1177/1073191117727346.

26. Verhage F (1983) Educational classification system for research purposes [revised version]. Internal publication Groningen, the Netherlands: Academic Hospital Groningen, State University Groningen.

27. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* 2009;10:459-466.

28. Hilverda K, Bosma I, Heimans JJ, Postma TJ, Peter Vandertop W, Slotman BJ, et al. Cognitive functioning in glioblastoma patients during radiotherapy and temozolomide treatment: initial findings. *J Neurooncol.* 2010 97:89-94.

29. Torres IJ, Mundt AJ, Sweeney PJ, Llanes-Macy S, Dunaway L, Castillo M, et al. A longitudinal neuropsychological study of partial brain radiation in adults with brain tumors. *Neurology.* 2003;60:1113-8.

30. Ismail MF, Lavelle C, Cassidy EM . Steroid-induced mental disorders in cancer patients: a systematic review. *Future Oncol*. 2017;13:2719-2731.

31. Rock PL, Roiser JP, Riedel WJ, Blackwell AD Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol Med*. *2013*;44:2029-2040.

32. Stern Y, Arenaza-Urquijo EM, Bartrés-Faz D, Belleville S, Cantilon M, Chetelat G, et al. Whitepaper: Defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimer's Dement*. 2018 (epub) doi: 10.1016/j.jalz.2018.07.219.

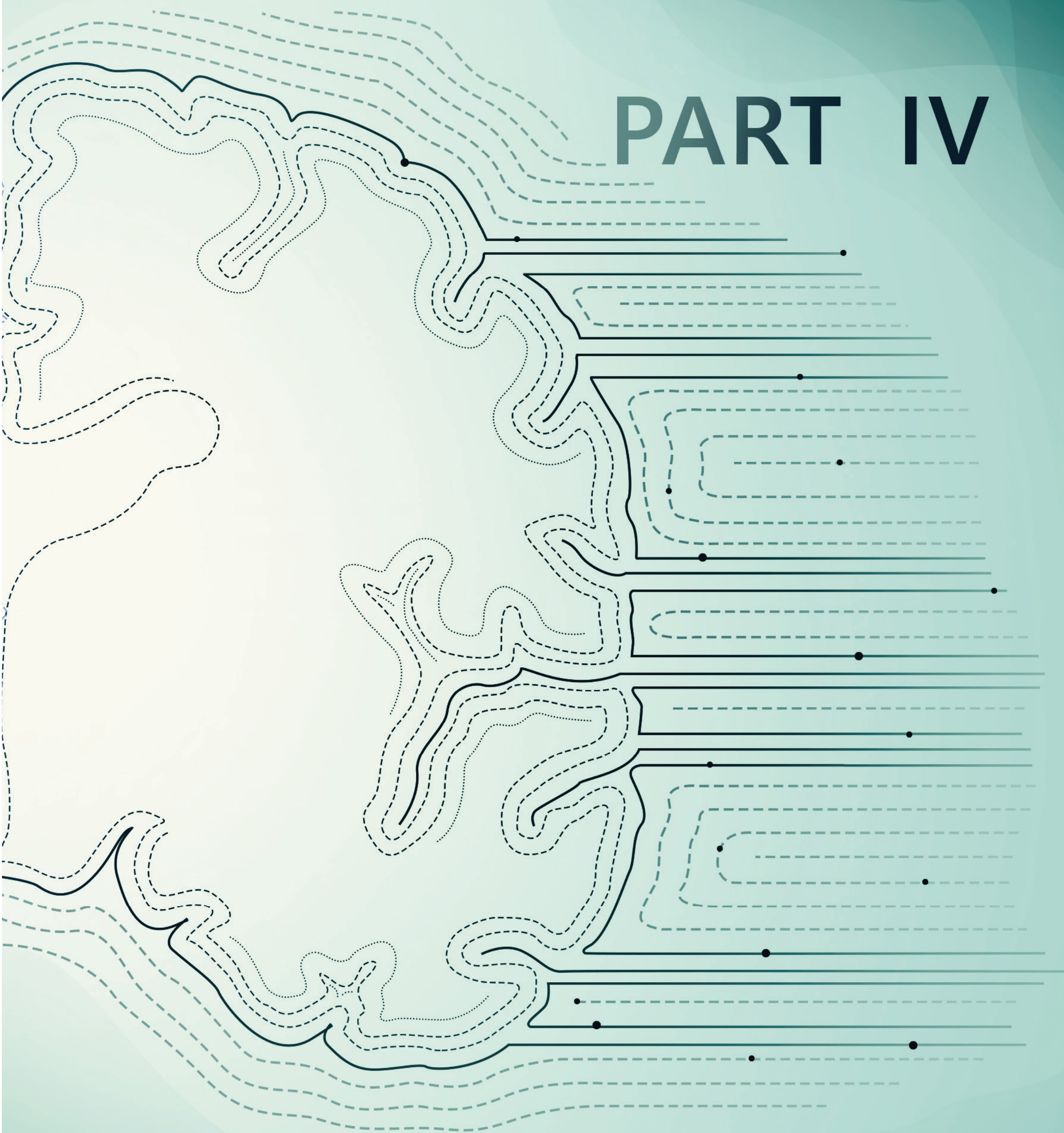
SUPPLEMENTARY TABLES

Supplementary Table 1. Description of neuropsychological tests

Test	Content	Scores and computation
CNS VS Verbal Memory (VEM) Test	Fifteen words are presented, one at a time. Subject subsequently identifies presented words among new words.	Total items correct
CNS VS Visual Memory (VIM) Test	Fifteen abstract images are presented, one at a time. Subject subsequently identifies presented images among new images.	Total items correct
CNS VS Finger Tapping Test (FTT): Motor speed	Subject presses space bar as quickly as possible for 10 secs (index finger, three trials per side).	Taps right average + taps left average
CNS VS Symbol Digit Coding (SDC) Test: Psychomotor speed	Participant matches numbers with corresponding symbols for two minutes.	Correct responses – incorrect responses
CNS VS Stroop Test: Interference	Part 1: subject presses space bar when a word is presented. Part 3: subject presses space bar if the color of the word does not match the meaning of the word.	(Reaction time Part 3 – Reaction time Part 1) / Reaction time Part 1
CNS VS Shifting Attention Test (SAT): Cognitive flexibility	Subject matches geometric objects by shape or color for two minutes.	Correct responses – Errors
CNS VS Continuous Performance Test (CPT): Vigilance	Subject responds to target letter among distractors for 5 minutes.	Average reaction time of responses to B
Digit Span Forward (DSFW) †: Attention	Subject repeats series of digits of increasing length.	Total items correct
Digit Span Backward (DSBW) †: Acoustic working memory	Subject repeats series of digits of increasing length in reverse order	Total items correct
Letter Fluency[a]: verbal (lexical) ability, executive control	Subject names words starting with a specific letter for 1 minute (3 trials total). Three alternate test forms were used.	Total words correct

† paper-and-pencil test

PART IV



CHAPTER 8

General discussion, considerations for clinical practice & directions for future research

The research described in this dissertation aimed to 1) contribute to our understanding of the nature of cognitive (dys-)function in patients with primary brain tumors undergoing surgical resection, 2) illustrate the value of postoperative cognitive measures for prognostic purposes, and 3) improve the alignment between needs and questions in clinical care and scientific research, by using clinically applicable and intuitive methodologies.

In PART II (**Chapters 2-5**), we investigated the prevalence of and patterns in cognitive dysfunction, as well as their correlates, in patients with non-functioning pituitary adenoma (NFPA, **Chapter 2**) glioma (**Chapter 4**) and meningioma (**Chapter 5**) one day before and, in **Chapter 2** and **5**, three months after surgical resection. We investigated the specific influence of APOE ε4 allele carrier status on pre-surgical cognitive impairment and cognitive change up to 12 months after resection in patients with newly diagnosed glioma or meningioma in **Chapter 3**.

PART III (**Chapters 6** and **7**) addressed the prognostic value of cognitive measures. In **Chapter 6,** we investigated whether cognitive impairment during early adjuvant treatment predicted survival duration in glioblastoma patients independent of known clinical prognostic factors. **Chapter 7** describes a longitudinal study that investigated whether decline on a personalized set of three neuropsychological tests predicted radiological disease progression according to RANO criteria in patients with anaplastic astrocytoma and glioblastoma.

The following section provides an overview and discussion of the core findings on the formulated goals, methodological considerations, and an evaluation of challenges and opportunities in current clinical practice and for future research.

1. Understanding the manifestation of cognitive dysfunction and its predictors (Part II of the dissertation)

1.1 Prevalence and course of cognitive dysfunction before and after treatment

Preoperative cognitive (dys-)function

Chapters 2-5 illustrate that patients with meningioma, glioma and NFPA show considerable risk of cognitive dysfunction before treatment. Our patient samples performed worse than sociodemographically similar healthy controls on the majority of, if not all, cognitive tests of the CNS Vital Signs battery (**Chapter 2** NFPA, **Chapter 3** glioma and meningioma).We consistently observed cognitive impairment in *at least* half of patients before surgical intervention across diagnoses. Specifically, 56% of patients with NFPA in **Chapter 2** showed impairment on at least one cognitive domain, while 57% of diffuse glioma patients in **Chapter 4** and 55% of meningioma patients in **Chapter 5** were assigned to clusters that characterized profiles with impairment. Although dysfunction may overall be more mild in meningioma,[1] our results suggest that similar percentages of meningioma and glioma patients harbor a cognitive profile with actual impairment before surgical intervention. At the same time, we also note that a substantial number of patients (44% of NFPA, 43% of glioma, 45% of meningioma) presented with a generally intact cognitive profile, despite the presence of a symptomatic tumor. Factors that may contribute to the (variance in) cognitive performances and profiles are discussed in *section 1.3 Predictors of cognitive performances and profiles*.

Postoperative cognitive (dys-)function

Postoperative status

Despite the mostly benign clinical course of NFPA and meningioma, and the general assumption that their resection is beneficial to cognition,[1] since a primary driver of dysfunction is removed,[2] the rates of impairment (**Chapter 2**) and impaired profiles (**Chapter 5**) three months after surgery were similar to those before surgery. Specifically, 63% of patients with NFPA showed clinical impairment on at least one domain of CNS Vital Signs and 45% of patients with meningioma were assigned to clusters that characterized profiles with impairment.

In regard to malignant tumors, **Chapter 6** strongly supports previous research[3,4] by showing that high grade glioma patients are often cognitively impaired after surgery. As many as 99 out of 114 patients (87%) showed impairment on at least one test measure, and 38 patients (33%) showed impairment on *at least half* of the tests. Although the glioma itself is also viewed as the main disrupter of cognition,[5] its removal does not necessarily result in relief of cognitive dysfunction.

Postoperative course

We investigated the relatively unknown individual courses of cognitive functioning of NFPA patients from before up to three months after endonasal endoscopic transsphenoidal surgery by using a Reliable Change Index (RCI). This RCI measure provides a more accurate indication of the change in performances of individual patients than previously used measures, such as differences in raw scores or standardized scores, as it takes both practice effects and (varying) test-retest reliability into account. Interestingly, the individual courses in the sample varied substantially, with equal proportions of patients (28%) showing cognitive decline or improvement, and 8% showing both improvement and decline. These individual variances were masked by group results that indicated overall performance stability over time. Cognition in NFPA patients has usually been studied on group level only, with studies suggesting overall improvement.[6,7] Our results show that we need to be aware that, similar to other PBT,[4,8] not all individual patients with NFPA benefit from surgery on a cognitive level and that group results cannot be directly translated into predictions for individual patients.

In the APOE-study in **Chapter 3** (a more elaborate discussion of this study can be found under section 1.3), we investigated the longitudinal course of cognitive functioning from the postsurgical assessment up to 12 months after surgery of glioma and meningioma with Longitudinal Multilevel Modelling, that estimates individual differences in patients' performances over time. We observed (small) overall improvements from the pre-surgical to 12 months postsurgical assessment on the majority of cognitive measures, with the exception of sustained attention (Continuous Performance test), visual memory (Visual memory test), attention and working memory (Digit Span Forward and Backward). Interestingly, the longitudinal course did not differ significantly between patients with meningioma and glioma (WHO grade II-IV), except for letter fluency and only in the interval from pre- to 3 months post- surgery. The similar trajectories may be partly attributable to the fact that glioma patients with disease progression and/or poorer clinical status do not return for follow ups (also reflected in the 17% of glioblastoma patients in **Chapter 6** that did not return as early as 3 months after resection), thus making our follow up glioma sample biased towards fitter, possibly younger, patients.

1.2 The nature of cognitive dysfunction: cognitive performances and profiles

The way in which cognitive dysfunction manifests, i.e., to what extent different domains are affected, can be studied in various ways. In **Chapter 2**, we applied a common approach by studying group- and individual level performances on domains separately. Similar to - relatively scarce - (prospective) literature on patients with pituitary adenoma who underwent resection,[7,9-12] NFPA patients showed pronounced disruption on tests of executive functioning. In light of studies using non-computerized (i.e., paper-and-pencil) testing in other PBT groups,[13,14] this finding supports the proposed vulnerability of more complex functions that involve larger distributed networks[5,15] to tumor disruption, regardless of the exact pathophysiology.

In **Chapters 4** and **5,** we provide a different framework by exploring patterns in impaired performances across cognitive tests with Latent Class Analysis (LCA). An overview of the *pre-surgical* impairment profiles identified in these studies can be found in Figure 1. It appears that the high prevalence on the domain executive function found in previous studies[16,17] can manifest in multiple cognitive profiles in both meningioma and glioma patients. In our research, it could present as isolated dysfunction or in combination with susceptibility to impairment of other functions. Memory impairment, that is also often found with a high prevalence,[18] may rather be restricted to a smaller number of profiles (isolated memory dysfunction and global dysfunction), for which chances of impairment may be very high.

Comparing cognitive profiles in meningioma and glioma patients

As can be seen in Figure 1, we observed both similar and distinct profiles of cognitive impairment in our meningioma and glioma patients. The profiles found in both groups involve seemingly opposite ends of the cognitive spectrum; the "*intact*" profile (low chances of impairment across tests) and the "*global disruption*" profile (high chances of impairment across tests). Striking are the similar proportions of patients that these profiles present in (±45% "*intact*", 13%"*global*" in both samples). Even with differences in pathophysiology and population characteristics (such as sex), meningioma and glioma patients scheduled to undergo surgical resection can thus show these similar profiles in similar rates.

Besides these two "opposed" profiles that presented in both samples, we found profiles illustrating different natures (*which* specific functions were affected) and severities of impairment (*how many* measures were affected and the *probabilities* of impairment) that presented in either the glioma or meningioma sample. Similar to the finding that preoperative deficits in separate cognitive domains can be related to tumor type,[19] so may some cognitive profiles. For example, a broad impairment profile with apparent underlying speed-related problems was present in glioma, but not meningioma. This finding fits in the general framework for consequences of brain injury (as opposed to compression), in which mental slowing is a key problem that contributes to problems in other domains.[20] Still, direct statistical comparisons of the diagnostic groups are imperative to investigate these differences further.

Cognitive profiles after surgery

Chapter 5 additionally investigated cognitive impairment profiles three months *after surgery* within the meningioma sample. Besides an "intact" profile that was similar in nature and proportion as the one before surgery, most post-surgical profiles ("verbal memory", "executive-speed", "(psycho-)motor-attention", "diffuse") appeared somewhat different from the ones identified before surgery. We emphasize here that pre- and postsurgical samples had comparable sample characteristics. This finding leads us to hypothesize that, although the prevalence of cognitive dysfunction may be similar after meningioma resection as before, the nature of dysfunction, and possibly problems that patients encounter in daily functioning, may be different.

It is important to note as well that about two-thirds of meningioma patients classified as “intact” before surgery, were also classified as “intact” after surgery, indicating stable unimpaired functioning. The other one-third apparently had *deteriorated*, as they were classified in one of the impairment clusters after surgery. Some patients seemingly *showed new deficits in addition to existing ones*, e.g., 29% patients went from the psychomotor-executive profile to the executive-speed profile. Conversely, 26-38% of patients from the pre-surgically impaired clusters was classified as “intact” after surgery, indicating that they had shown *recovery*. An important finding that also reflects the added value of LCA, is that we found patients who showed a *qualitatively different* cognitive profile, e.g., 19% of patients with a “(pyscho-)motor-executive” profile before surgery showed a “verbal memory” profile at after.

1.3 Predictors of cognitive performances and profiles

Findings from **Chapters 2-5** support the proposed multi-dimensionality[2] of factors influencing cognition in PBT. Moreover, an insight we gained beyond what is known from literature is that some factors previously related to separate cognitive domains may actually discriminate between an intact versus a (broadly) impaired cognitive profile, while others may help to discriminate between different impaired profiles. In this section, we discuss the predictive value of the investigated patient, disease and germline genetic factors.

Patient factors

Sociodemographics: consistent prediction of intact cognition

Even though test performances used in our studies were already standardized for effects of age and educational level found in healthy individuals,[21] these factors seem to show additional influences on cognition in PBT patients (**Chapter 4** and **5**). Intact and milder profiles (isolated executive dysfunction in glioma, isolated verbal memory dysfunction in meningioma) were related to younger age compared to more severely disrupted profiles. This suggests that, with higher age, the chance of more severe dysfunction that involves multiple domains may be higher. The nature of the dysfunction may still vary.

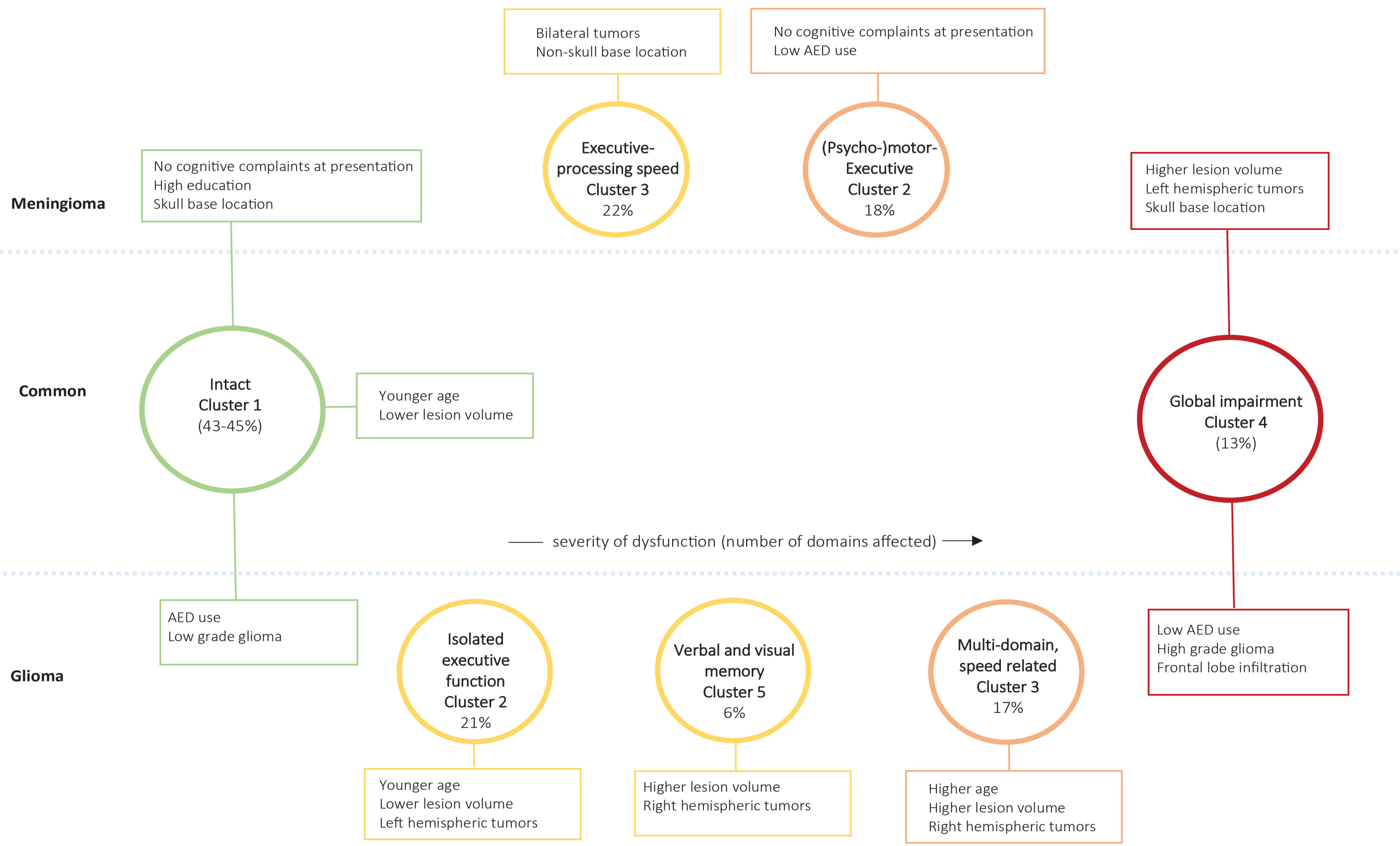


Figure 1. Cognitive phenotypes before surgery with corresponding predictors, based on Chapters 4 and 5. Profiles and predictors thereof in the glioma sample are displayed in the lower section of the figure, in meningioma in the upper section, and the middle section contains those found in both samples.

In meningioma patients, 50% of the "intact" cluster had a high education level. Educational attainment may reflect lifetime exposures that are related to higher cognitive reserve,[22] i.e., a higher ability of the brain to actively cope with damage by means of compensatory processes,[23] apart from tumor characteristics that can already influence reorganization.[24] Sociodemographic factors are easy to collect as part of a clinical examination, and may be used for a quick indication about a patient's (relative) likelihood of having an intact cognitive profile and thereby unimpaired communicative and decision-making ability.[25,26]

Symptoms of depression: low burden in patients with an intact profile

It is known that various biological (e.g., inflammatory[27] and neurotrophic)[28] and behavioral (e.g., apathy)[29,30] depression markers can mediate cognitive fitness. In **Chapter 5**, we found postoperative scores on the Depression facet of the Hospital Anxiety and Depression Scale to be significantly lower in the patient cluster that showed an "intact" profile compared to all other clusters. The "(psycho-)motor-attention" cluster showed the highest Depression score. We can explain this finding when we take into account that psychomotor slowing is a diagnostic criterion for depression in the DSM-V,[31] and that disruption of (networks involved in) sustained and divided attention[32] has been reported in depressed individuals. Moreover, as some of the biological and behavioral processes found in depression are also linked to tumor activity,[33] and co-occuring cognitive impairment and depression has been linked to worse survival outcome,[34] monitoring depressive symptoms of patients at clinical follow up is warranted.

Disease factors

Tumor characteristics: discriminating between impaired profiles before surgery

Smaller *tumor volume* was related to an intact pre-surgical cognitive profile in both of our samples in **Chapters 4** and **5**, which supports previous findings in glioma,[35] meningioma[36] and cerebral metastases.[37] Mass effect can apparently disrupt cognitive networks independent from other tumor features, such as infiltrative potential. We also note that the degree of peritumoral edema may play an additional role here as well,[38,39] but we did not investigate this.

Further in accordance with findings on separate tests,[17,40,41] there was a propensity towards *high grade* lesions (WHO III/IV) in the "globally disrupted" cognitive profile of glioma patients. L*ow grade* lesions (WHO II) were most common in the "intact" profile. This difference may be partly attributed to differences in growth patterns. Slower growing, low grade lesions allow for 1) more functional remapping - by involving perilesional areas or more remote areas in the same or the contralateral hemisphere - and 2) for some function to persist in the tumoral tissue.[24] WHO grade was not related to cognitive profiles in our meningioma sample. This may be due to a less pronounced difference in growth pattern between benign and atypical meningioma, but we also note that the number of atypical tumors was small (8%).

Our findings with regard to the predictive value of tumor locations in glioma (**Chapter 4**) are in part supported by previous investigation, but are also somewhat different. One example regards the effect of *lateralization*. Habets concluded from several empirical investigations[15,35] that left hemispheric glioma were associated with worse cognitive deficits on tests.[5] We found left hemispheric glioma to be associated with an isolated executive impairment profile, while right hemispheric glioma were related to a speed-related impairment profile that affected more domains. At first sight, this appears contradictory. At the same time, executive dysfunction is related to left hemispheric lesions.[17] and a speed-profile fits to reporting[42] of patients with right hemispheric damage (from stroke) showing more pronounced slowing of information processing than patients with left hemispheric lesions. We also note that neuropsychological tests often carry a language component (e.g. instructions, responses) apart from the test content, and this may also partly explain stronger disruption in left hemispheric lesions. *Frontal lobe* glioma were more common in the global disruption profile in glioma patients, which warrants awareness that glioma infiltrating networks involving the frontal lobe may have a widespread influence on patients' cognition beyond, e.g., executive functions.

Substantial inconsistencies exist in literature on the relationship between tumor *lateralization* and the degree of cognitive dysfunction in the meningioma population. Our finding in **Chapter 5** that left-sided meningioma were related to the global impairment profile before surgery are in line with several studies reporting more deficits in this group before and or after treatment[14,39,43], although other studies found no significant differences as compared to right sided lesions.[36,44,45] Interestingly, meningioma located at the supratentorial skull base were as prevalent in the intact as the globally disrupted profile in our study, whereas previous investigation found a relationship between skull base adhesion and worse performance on cognitive tests.[43] These different findings call for more investigation into the relationship between anatomical locations of meningioma and pre-surgical cognition. We note that anatomical locations of meningioma are usually broadly categorized for research purposes, and that further distinctions, e.g., within infratentorial locations and supratentorial skull base locations, may reveal specific deficits that were not captured in our and previous studies. Still, with the exception of bilateral tumor location, most meningioma location variables were not predictive of postsurgical cognitive profiles. Location may play a smaller role at this time point compared to before surgery, especially if the pre-surgical effect was mediated by local edema.

Suprasellar extension and pituitary hypofunction in NFPA

In **Chapter 2**, we found no effect of *suprasellar growth* of NFPA on cognitive performances. This finding contradicts reporting by Psaras and colleagues, who found that removal of the suprasellar extension was the primary factor contributing to cognitive improvement after surgery.[12] NFPA frequently present with suprasellar extension that can compress adjacent structures, such as the third ventricle and hypothalamus, and subsequently induce cognitive (e.g., memory) dysfunction.[46,47] We hypothesize that the Hardy-Wilson category of tumor extension, although relatively easily obtained from coronal MRI as part of regular anatomical classification, may not be precise enough for predicting cognition. A 3D volumetric report of the suprasellar portion of the tumor may be more appropriate.

Patients with *loss of functioning of the pituitary-adrenal and/or pituitary-thyroid axes* performed better on verbal memory than those without loss of functioning in these axes. Usually, dysfunction of these hormonal axes is related to decreased memory function, [48,49] making this a remarkable finding. Still, taking into account that all patients were receiving suppletion at time of cognitive assessment, this could have boosted memory performance as compared to other patients with subtotal (i.e., milder) hypofunction not receiving suppletion.

Symptomatology at time of presentation: possibly differential effects in glioma and meningioma

Notably, the effect of treatment with *anti-epileptic drugs* (AED) on pre-surgical cognition was different in glioma and meningioma patients (see **Chapter 4** versus **5**); It was a predictor of an intact cognitive profile in glioma, but of an impaired ("psychomotor-executive") profile in meningioma. This finding contradicts reporting that epilepsy (treatment) is related to worse cognition in both diagnoses.[14,50] Mechanisms of tumor-related epilepsy are plentiful and are assumed to vary between infiltrative, intra-axial tumors versus distortive, extra-axial tumors.[51] Moreover, epilepsy in glioma is also indicative of low grade lesions,[52] which in turn are associated with less cognitive disturbances than high grade lesions.[17] Still, as AED use independently contributed to discrimination between pre-surgical cognitive profiles in our studies, there may be an interplay between the mechanism(s) of epilepsy and/or its treatment and functioning of networks that subserve cognition.

Cognitive complaints reported by patients at time of presentation were not indicative of the degree or nature of "objective" pre-surgical cognitive dysfunction in our glioma sample (as measured with tests). However, in meningioma patients, the "intact" pre-surgical profile was related to a very low proportion of cognitive complaints (only 6%, compared to, e.g., 32% in the group with global disruption). It is known that the level of subjective cognitive function as indicated on self-report instruments is only weakly related to objective performances on tests in PBT.[53,54] This may be due to the difference in what and how these approaches measure cognition (i.e., objective performances on neuropsychological tasks in a controlled setting or subjective experience of functioning in daily tasks). At the same time, whereas objective testing may be less ecologically valid, the internal validity of subjective reporting can suffer under a possible lack of insight of patients into their own level of functioning that isnot uncommon in (right sided) frontal and anterior temporal lesions.[55] Still, for clinicians, it is important to note that, in the triad of *objective measuring* vs. *self report on instruments* vs. *spontaneous reporting*, meningioma patients who spontaneously report cognitive problems at time of clinical presentation are more likely to display a profile with objective impairments.

APOE ε4: no evidence for effects on cognitive functioning before and shortly after treatment

Literature on APOE allelic variation and cognition in PBT lacks investigations of pre-treatment status. Our first hypothesis in **Chapter 3** was that APOE ε4 carrying meningioma and glioma patients would show worse cognitive performances and more impairment than non-carrying patients before surgery. This hypothesis was based on ApoE4's facilitation of maladaptive responses to CNS damage and less efficient modulation of myelin formation and repair,[56-59] that proposedly negatively modulates cognitive functioning.[60-62] Our findings showed no significant differences between carriers and non-carriers. We hypothesize that, as tumor-related injury develops more gradually over the years, carriers may have been able to compensate for the reactive changes and the less efficient network organization,[61,63] thereby showing similar performances as compared to their non-carrying counterparts. A key question to be studied here is whether deviant functional brain activation patterns can be observed in ε4 carrying PBT patients with similar task performance(s) as non-carriers. In addition, it is argued that the ε4 relates to a "cognitive phenotype" because of effects on white matter integrity.[61] We did not adopt ε4 carrier status in our pre-surgical LCA's, because genotyping was only available for a subset of patients (until September 2017), but its relationship with cognitive profiles can be investigated in future studies.

We expected the longitudinal course of cognition in carriers to be worse than in non-carriers, based on the interaction between APOE ε4 and oncological treatment effects[64,65] as well as findings on cognitive performances in patients treated for (non-) CNS cancers.[62,66,67] However, in our study, PBT patients who carried the APOE ε4 allele did not show a significantly worse trajectory of cognitive functioning over the course of surgical and adjuvant treatment, at least in the first year after surgery.

Previous studies that did find a negative relationship between ε4 allele presence and cognition, assessed performances years after completing treatment.[68,69] E4's interaction with anti-tumor treatment may manifest in cognition on the longer term. This may especially be true for glioma undergoing a long trajectory of adjuvant treatment with concurrent chemoradiation followed by chemotherapy. Still, research into germ-line genetic factors in relation to cognitive performance of PBT patients is in a relatively early stage.[70] Investigations of APOE at later follow ups in large patient samples that allow for stratification according to possibly relevant genetic (e.g, COMT)[70] and patient moderators (e.g., sex[71] and smoking),[72] and involving functional imaging should shed more light on its relevance.

2. THE PROGNOSTIC VALUE OF COGNITIVE MONITORING IN POST-SURGICAL CARE FOR HIGH GRADE GLIOMA (PART III OF THE DISSERTATION)

Clinical characteristics, primarily patient age and functional performance status (Karnofsky Performance Status, KPS)[73,74] are often used to explain heterogeneity in survival outcomes that exists in patient groups with similar histological diagnosis. The prognostic value of these factors lies in their indication of physical fragility and, in case of KPS, also disease activity.[75] Still, their effects on survival outcome can be confounded by other factors,[76] such as (salvage) treatment decisions. Fact is that survival outcome is still heterogeneous within subgroups of patients stratified by clinical prognostic factors.[74]

Cognitive performance - and changes therein - are also increasingly viewed as a possible reflection of the degree of disruption of cerebral networks due to tumor-induced infiltration, mass effect and edema (i.e., parameters of disease activity). Attention towards its value in prognostic stratification, mostly in high grade glioma, is therefore growing.[76] Still, several important questions regarding the use of cognitive parameters for prognostic purposes have to be addressed:

First, it should be evaluated *for what purpose(s) we can use measures of cognition*. In PART III, we investigated its value for early prognostic stratification (knowing which patients may be at risk for shorter survival and therefore warrant extra vigilance in clinical follow up), and for longitudinal disease monitoring (using cognitive monitoring as an addition to general follow-up care). Second, as high-grade glioma and their cognitive effects are heterogeneous, we should ask *how we should assess cognition for prognostic purposes*. This primarily involves decisions on assessment content and whether neuropsychological evaluation should involve uniform testing with a core test set, e.g., based on overall vulnerabilities in the population, or if there should be some form of assessment personalization based on patient or tumor characteristics.

2.1 Early refinement of prognosis

It is well known that, over the course of treatment for glioma, patients can show decline in cognitive functioning or develop new cognitive deficits.[2,77] These deficits may be the result of treatment related damage and toxicity,[64,78] but there are also indications that early post-surgical deficits before adjuvant treatment may already indicate poorer prognosis.[79] In **Chapter 6**, we focused on the question whether impairment on measures obtained in the early adjuvant treatment phase for glioblastoma, when patients return to the outpatient clinic for standard care appointments, can be used for prognostic stratification. In a sample of 114 patients, impaired performances on tests measuring executive control and simple processing speed (Stroop tests I and III, reaction times) predicted substantial reductions in survival time of ±25%. This effect existed even when controlling for the effects of known prognostic factors KPS and age, but also for the effect of salvage treatment, which is a factor that has been left out of studies on cognition and survival thus far. Furthermore, as the presence of early impairments was related to less salvage treatment administration, the importance of taking incorporating this factor for survival prediction with cognitive measures is further emphasized.

In conclusion, patients' *cognitive status* on two uniform tests, that take around 5 minutes to administer, at an early postsurgical clinical evaluation may be an easily obtainable prognostic indicator.

2.2 Longitudinal, personalized monitoring

A challenge in using cognitive *change* over time as a tool for predicting (subsequent) disease progression, is that the cognitive functions that are most sensitive to changes in disease activity differ between, and can therefore be hard to capture in, individual patients. Some studies have attempted to capture individual variability in sensitivity, for example by tailoring test selection to tumor location.[80] Still, as glioma tend to affect brain functioning outside their direct location,[24] a location-based selection may not fully cover the existing individual variation. Additional methodological challenges in longitudinal monitoring are the absence guidelines for *how to measure change* in cognitive performances in individual patients specifically for prognostic purposes , and which *cut off value for "cognitive decline"* we should use here.

The study described in **Chapter 7** was unique in 1) its approach to the personalized selection of tests used in follow up monitoring, and 2) its use of the Reliable Change Index to measure change as part of a prognostic longitudinal study. We hypothesized that immediate post-surgical improvements in cognition may provide important information about which cognitive domains are most sensitive to tumor presence, and therefore tumor recurrence at a later time point. Patients underwent three-monthly assessments together with standard clinical follow-up until radiological progression was established or up to 24 months after surgery.

For each patient, we opted to select the *three functions for which they showed the most relief - the highest RCI values - within 3 months after surgery* for follow up monitoring in our analyses. We calculated changes in performance on the three personalized tests using the first postsurgical assessment (T3) as baseline (e.g., interval T6-T3, T9-T3, etc), with an RCI of ≤-1 on at least two of the three tests in an interval considered cognitive decline. We found that the majority (60%) of patients with progressive disease (PD) displayed decline on their personalized set of tests before or at time of radiological PD, and that the majority (80%) of patients with stable disease during follow up remained stable on their set of tests. Moreover, the chance of PD in case of cognitive decline on this set was 5 times as high in case of stable performance. This effect was higher than the one found in previous investigation in a HGG sample with uniform testing[81] (also using three tests) and similar to the one found in a tumor location-based selection of tests in a heterogeneous PBT sample (using five tests).[80]

We conclude from this study that patients' *change* on a brief, personalized assessment may serve as a noninvasive indicator of disease status over time, and should be further studied in a larger sample.

3. METHODOLOGICAL CONSIDERATIONS

3.1 Neuropsychological assessment

Assessment content

A limitation across our studies concerns the content of the neuropsychological assessment. For integration in the clinical trajectory, a balance had to be guarded between keeping the assessment short enough for integration with other standard care appointments (e.g., MRI, consultation with treating clinicians) and the importance of testing a range of cognitive domains. Computerized testing has multiple advantages in this matter, as it can be less time consuming (the assessment itself, but also due to automatic score computation), items are picked at random (thereby automatically presenting alternate test forms for repeated assessments), and precise measurement of reaction times.[82] At the same time, multiple limitations can be noted regarding the tests of the CNS Vital Signs battery specifically.

First, the memory tests of the test battery assess immediate and delayed recognition of verbal and visual material, but there is no assessment of the learning curve nor of free recall. These functions may in fact be the most important facets to test[83] as they show high dysfunction rates and stronger prognostic value than recognition.[79] Our estimation of memory problems may be lower than is actually the case in the true PBT population.

In general, computerized tests may put a higher strain on information processing speed than traditional paper and pencil tests. In translating tests to computerized versions, the item presentation and/or the response is often timed, while in the 'traditional' version this may not be the case. For example, we can compare the CNS Vital Signs' Verbal Memory test and Stroop tests to non-computerized counterparts Hopkins Verbal Learning Test and Stroop test. In the original forms, patients *do not have to* respond within a couple of seconds to each item, as opposed to the computerized forms. In the original Stroop test, the total time it takes for a patient to complete the test is recorded, but no item average. What this means is that there is a risk with CNS Vital Signs that mental slowing affects performances on tests that claim to measure other functions. At the same time, we do note that our LCA (**Chapter 5**) showed that there are distinct clusters with and without impairment on simple processing speed, indicating that mental slowing may not automatically disrupt all CNS Vital Signs tests.

A majority of tests in our protocol have a language component with regard to their items, the required response, or both. However, we did not specifically test language abilities, such as naming and language reception. Aphasia symptoms can be a presenting symptom of PBT. It can also occur temporarily after tumor resection[84] in varying degrees. Language testing is recommended, especially in case of specific lesion locations,[84] as subtle problems in language reception or expression may affect test performance without the cognitive ability itself being disrupted.

Assessment timing

In order to ensure uniformity in timing of the assessments and facilitate integration, our pre-surgical assessment took place one day before surgery, which is the day of hospitalization. Although this timing had advantages from a logistical standpoint, we note that anxiety regarding undergoing surgery may have influenced cognition, although there was no evidence found for this in an earlier study in a subset of patients from this cohort.[85] Furthermore, as patients undergo multiple appointments the same day, assessment sometimes needed to be cut short, thereby providing incomplete data. If assessment took place after multiple appointments, fatigue could also have influenced patients' performances.

The assessments in the studies described in this thesis were repeated up to 3 or 12 months after surgery. As mentioned in **Chapter 3**, late effects of adjuvant treatment can continue beyond these time points.[78] Specifically with regard to the interaction between these late effects and APOE ε4 allele carrier status, longer-term follow up assessments may have provided additional information. Measurements at 24 months post-surgery are currently part of the research protocol at the Neurosurgery department of Elisabeth-Tweesteden Hospital, but due to later implementation (2015 onwards) and a lower proportion of (glioma) patients who return or this measurement, this time point was not adopted in our current studies.

3.2. Patient samples

Several biases may exist in the patient samples of the described studies. First, all patients underwent surgical resection. This means that our results cannot be generalized to *patients following a different care path*, e.g., those undergoing biopsy and/or systemic treatment only or those with (incidentally discovered) tumors in a wait-and-see trajectory. The latter group of patients are currently understudied, even though they likely also show cognitive dysfunction[86] possibly depending on tumor location.[87] In a new research program at the ETZ (Topklinische Zorg en Onderzoek 2020-2024), neuropsychological testing and advanced MR imaging will also be routinely performed in patients who do not undergo surgery.

We also address potential sample bias due to *participation refusal for follow ups*, e.g., for relatively intense follow up like in **Chapter 7**. As mentioned, as much as 50% of patients asked to participate in our disease monitoring study in **Chapter 7** refused for various reasons, including the anticipated intensity of follow up. If patients feel that three-monthly assessments are too burdensome, this may reflect patient or disease characteristics, such fatigue or distress. In addition, *drop out* between measurements over time, as seen in **Chapters 2, 3, 5-7** is a common phenomenon in patients with cancer. As many as 31 of 179 glioblastoma patients in **Chapter 6** who underwent pre-surgical assessment did not return 3 months after surgery due to deterioration in clinical status or early death. This suggests that missing cases on follow up assessments were not simply random. We acknowledge that our post-surgical (glioma) samples in **Chapter 3** and **6** are probably biased towards younger, fitter patients. At the same time, as T0 and T3 measurements were part of regular clinical care, the dropout may reflect the 'natural' flow of patients who show early clinical deterioration and for whom prognostication and cognitive assessment may not be as relevant.

4. CHALLENGES AND OPPORTUNITIES IN CLINICAL PRACTICE AND FUTURE RESEARCH

4.1 Alignment between clinical care and research - using clinically intuitive methodological approaches

Multiple factors may play into under-recognition of cognitive dysfunction in care,[88,89] including a lack of awareness and prioritization by both patients and staff. To show the potential value of neuropsychological assessment for daily neurosurgical care, we stress the importance of aligning methodology in research with *what clinicians actually want to know* and, closely related, *if the derived results are intuitive for a clinical setting*. This concerns instances where we measure cognition as a part of treatment outcome as well as instances where it is used for the purpose of predicting disease outcomes.

One example of the latter is that, for clinicians who want early prognostic information for patients with dismal survival outcome, it makes more sense to know how a characteristic relates to survival duration as opposed to how it relates to (chances of) of death. A method like Accelerated Failure Time modeling is relatively underused in medical research. However, it allows for derivation of a Time Ratio that is directly interpretable for health professionals who may not be familiar with risk indicators. If the question is whether cognitive decline from one time point to the other reflects an event like increased tumor activity, reporting a Hazard Ratio can provide the necessary information, as it conveys an increase in chance of the event on which clinicians could act at that time.

In regard to cognition as an outcome, we addressed that investigating profiles as opposed to test performances may provide a better understanding of cognition on a fundamental level. There are multiple arguments as to why investigating profiles is also more clinically applicable. A neuropsychologist may look at a patient's integrated cognitive profile instead of looking at one test when evaluating the need for further assessment, strategy training or rehabilitation. Knowing to which cognitive profile a specific patient or disease characteristic is related is in that case also most relevant. Moreover, it is crucial for neuropsychologists to know *which tests are and which tests are not sensitive to dysfunction in a specific patient population*. The fact that a large proportion of patients shows impairment on a specific test in a population does not necessarily mean that the test is sensitive in the sense that it *discriminates between different cognitive profiles*. Methods such as LCA allow us to simultaneously provide an integrative analysis of (trajectories of) latent cognitive profiles and estimation of contributions of different tests to the discrimination between these profiles.

4.2 Considerations for clinical practice

Implications of cognitive deficits in patients for clinicians

In order to improve the recognition of cognitive dysfunction,[90] it is important for clinicians to be aware of how common cognitive deficits are. Our findings indicate that over 50% of patients scheduled to undergo resection display objective cognitive impairment. About 10% may display impairment across domains and the other 40% may show various severities and natures of impairment that also depend on patient and disease characteristics. Surgical treatment of PBT does not necessarily resolve cognitive dysfunction, but dysfunctions may be different after the tumor is removed.

As mentioned, cognitive deficits can widely affect daily functioning of patients. At the same time, the presence and type of cognitive dysfunction a patient harbors is also relevant for various aspects of a clinician's job. For example, patient communication should be approached differently in memory dysfunction versus mental slowing. Different objective dysfunctions may also relate to different problems in daily life, and this could be taken into account in patient informing. For example, deficits in mental and psychomotor speed may also affect a patient's driving ability. Discussing such practical implications of cognitive deficits can help manage expectations of patients and adjust their goals after treatment. In addition, specific dysfunctions can impair a patient's ability to engage in decision making regarding treatment.[26] As decision making in neurosurgical care moves more towards a shared consensus between physician and patient, the latter issue will become increasingly important in the future. It should be noted overall that not all patients experience objective deficits as a problem.[91] Assessing the subjective level of burden due to cognitive dysfunction is therefore relevant.

Adaptability and efficient use of assessment

A core testing protocol for the PBT population has been recommended by the RANO group[92] for the purpose of cognition as outcome evaluation, but this set is probably not enough the capture the full extent of (dys-)function. In outcome assessment, it may be useful to administer such a core set along with patient- or disease-specific additions, e.g., tests of language in case of tumors in eloquent areas,[84] or of processing speed in case of right-sided lesions or older patients.[93,94] For predicting the degree and nature of dysfunction in PBT patients, clinicians should be aware of characteristics on patient as well as disease level before surgery. After surgery, patient characteristics, such as age, educational attainment and depressive symptoms, may be more useful for estimating risks of cognitive impairment than disease factors, such as tumor location. Importantly, many useful characteristics may already be obtained as part of routine care. Pre-surgical cognitive fitness is quite a strong predictor of post-surgical performances[16,95] and in some patients with malignant tumors, it also reflects their best cognitive state during their disease.[96] Therefore, a broad pre-surgical assessment does seem particularly relevant, with possible targeting of potential risk domains at later follow ups.

Obtaining cognitive data requires extra effort in the care trajectory. Using the data to its full potential is therefore important. As mentioned in the introduction of this dissertation, cognitive functioning is related to many facets of daily life. For neuro-oncologists, it can be of particular interest that routinely obtained cognitive measures can serve prognostic purposes as well. If cognition is used as additional means for disease monitoring, our studies support that assessment needs to balance efficiency with accuracy of testing. Broad or uniform testing may therefore be less appropriate here. Broad testing protocols may be deemed feasible for longitudinal follow up,[96] but they are strenuous for already vulnerable patients, may ultimately decrease motivation for participation, and are simply harder to integrate in the care trajectory. Moreover, 50% of tests in a general battery may not be sensitive to progression.[96] As mentioned, a limited set of specific tests may serve as early postoperative prognostic indicator (**Chapter 6**), and a set of personalized tests appears to convey an indication as to whether a patient is at increased risk for disease progression (**Chapter 7**). Cognitive follow ups that we obtain for prognostic purposes could therefore be shorter and more targeted than those used as outcome measurement.

4.3 Directions for future research

Cognition is a difficult phenomenon to study due to 1) the brain networks that underlie the various functions are complex and not yet fully characterized, and 2) its vulnerability to disruption in response to disease-, treatment- and patient-level factors. As a consequence, a multidisciplinary approach is critical for adequate study and understanding. We identify potential targets for future research.

Exploring dynamic patient characteristics for optimizing cognitive fitness

Many of the predictors we researched in our studies constitute static disease or patient characteristics (age, educational attainment, lesion location). However, physical and behavioral modifiable features of the roughly 50% of patients who were unlikely to suffer impairment could be investigated as part of a more rehabilitation-focused view on cognition. Depressive symptomatology is an example of such a factor, but other characteristics, e.g., physical activity, may also be relevant. Gehring and colleagues showed in a recent Randomized Controlled Trial that patients with WHO grade II/III glioma who participated in a 6 months home-based exercise intervention (of moderate to vigorous intensity 3 times a week) showed better scores on measures of attention and information processing speed, verbal memory and executive functioning.[97] Moreover, dietary patterns[98] and obesity[99] may be also related to cognitive trajectories. Some information about potential dynamic factors is generally obtained as part of routine clinical care. Self report, experience sampling methods or, regarding exercise, wearables may also provide opportunities for measurement.

Novel approaches to studying cognition

From “decline” and “improvement” to “qualitative change”

A second opportunity regards our frame of reference when it comes to research into cognition over time. Traditionally, the central question posed is whether PBT patients show improvement, decline and/or stability in functioning over time in cognitive domains. Findings from **Chapter 5** suggest that some patients change over time from one cognitive profile to another cognitive profile, and this has implications for our approach to studying cognitive change. For example, if a patient shifts from a profile with executive dysfunction to a profile with memory dysfunction, this cannot simply be judged as a “decline” or an “improvement”. Instead, it engenders a qualitative change in the cognitive profile. Such qualitative changes cannot be captured with traditional analyses. Longitudinal applications of classification models, such as latent transition analysis, can allow for the investigation of a patient’s probability for transitioning from one cognitive profile to another one over the course of surgical and oncological treatment. Results from such analyses are likely to provide new insights that are also clinically intuitive.

Data-driven development of a classification tool

Collecting sufficiently large datasets to perform data-driven analyses or model-based clustering in PBT research is not just a logistical challenge, but also requires data collection and funding over a timespan of multiple years often beholden to large treatment centers or multi-center collaborations that come with their own challenges. However, common prediction methods applicable to modest datasets cannot capture the interdependency between various dimensions of brain tumor symptoms, such as cognition, but also mood anfatigue, that have proven to be hard to explain thusfar. Machine learning applications that are data-driven (as opposed to model-based) are increasingly recognized for their value in (predictive) personalized neurosurgical care.[100] Machine learning may serve clinical practice through development of a classifier tool to predict cognitive functions, e.g., as also done for the detection of dementia in primary care.[90] Such a tool could use routinely obtained characteristics to estimate a patient's cognitive risk before and after surgery. Currently, efforts are made towards integration of machine learning methods in predicting cognitive outcomes for data from PBT patients who underwent craniotomy at Elisabeth-Tweesteden Hospital under the Topklinische Zorg en Onderzoek 2020-2024 protocol, and their added value will be investigated as part of new research projects over the coming years.

5. CONCLUSION

Cognitive dysfunction is a common symptom of benign and malignant primary brain tumors that may linger after treatment with roughly similar prevalence at group level, but possibly with qualitatively different manifestations in the individual patient. Patient- and disease-level characteristics each contribute to can specific cognitive deficits or profiles, whereas the influence of APOE allelic variation may be limited, at least before and in the first year after diagnosis. Brief, targeted cognitive measures after surgery may aid in early prognostic refinement and in longitudinal disease monitoring. We propose to broaden the framework for studying cognition in three main ways; 1) from investigation of test performances to cognitive profiles that combine performances on various tests, 2) from improvement, stability and decline in performances over time to qualitative changes in cognition over time, and 3) from outcome measure to a measure with a multifaceted value that potentially includes refinement of prognosis. Opportunities for future research may lie in usage of sophisticated data-driven analyses that can provide an integrated account of cognitive profiles and aim to deliver (classification) tools for clinical practice.

REFERENCES

1. Meskal I, Gehring K, Rutten G-JM, Sitskoorn MM. Cognitive functioning in meningioma patients: a systematic review. *J Neurooncol.* 2016;128(2):195-205.
2. Taphoorn MJB, Klein M. Cognitive deficits in adult patients with brain tumours. *Lancet Neurol.* 2004;3(3):159-168.
3. Habets EJ, Kloet A, Walchenbach R, Vecht CJ, Klein M, Taphoorn MJ. Tumour and surgery effects on cognitive functioning in high-grade glioma patients. *Acta Neurochir (Wien).* 2014;156(8):1451-1459.
4. Hendriks EJ, Habets EJJ, Taphoorn MJB, et al. Linking late cognitive outcome with glioma surgery location using resection cavity maps. *Hum Brain Mapp.* 2018;39(5):2064-2074.
5. Habets EJJ. *Neurocognitive functioning and health-related quality of life in patients with brain tumors (dissertation).* The Netherlands: Department of Neurology, Leiden University Medical Centre; 2020.
6. Wang X, Tong X, Zou Y, Tian X, Mao Z, Sun Z. The impact on cognitive functions of patients with pituitary adenoma before and after surgery. *Neurol Sci.* 2017;38(7):1315-1321.
7. Hendrix P, Griessenauer CJ, Hans E, Simgen A, Oertel J, Karbach J. Cognitive function surrounding resection of nonfunctioning pituitary adenomas with suprasellar extension: A prospective matched-control study. *J Clin Neurosci:* 2017;40:109-114.
8. van Loenen IS, Rijnen SJM, Bruijn J, Rutten G-JM, Gehring K, Sitskoorn MM. Group Changes in Cognitive performance after surgery mask changes in individual patients with glioblastoma. *World Neurosurg.* 2018;117:e172-e179.
9. Mussig K, Besemer B, Saur R, et al. Deteriorated executive functions in patients with successful surgery for pituitary adenomas compared with other chronically ill patients. *J Int Neuropsychol Soc.* 2011;17(2):369-375.
10. Mussig K, Leyhe T, Besemer B, et al. Younger age is a good predictor of better executive function after surgery for pituitary adenoma in adults. *J Int Neuropsychl Soc.* 2009;15(5):803-806.
11. Brummelman P, Elderson MF, Dullaart RP, et al. Cognitive functioning in patients treated for nonfunctioning pituitary macroadenoma and the effects of pituitary radiotherapy. *Clin endocrin.* 2011;74(4):481-487.
12. Psaras T, Milian M, Hattermann V, Gerlach C, Honegger J. Executive functions recover earlier than episodic memory after microsurgical transsphenoidal resection of pituitary tumors in adult patients--a longitudinal study. *J Clin Neurosci.* 2011;18(10):1340-1345.
13. Wefel JS, Noll KR, Rao G, Cahill DP. Neurocognitive function varies by IDH1 genetic mutation status in patients with malignant glioma prior to surgical resection. *Neuro-oncology.* 2016;18(12):1656-1663.
14. Dijkstra M, van Nieuwenhuizen D, Stalpers LJA, et al. Late neurocognitive sequelae in patients with WHO grade I meningioma. J *Neurol Neurosurg Psychiatry.* 2009;80(8):910.
15. Habets EJJ, Hendriks EJ, Taphoorn MJB, et al. Association between tumor location and neurocognitive functioning using tumor localization maps. *J Neurooncol.* 2019;144(3):573-582.

8

16. Rijnen SJM, Meskal I, Bakker M, et al. Cognitive outcomes in meningioma patients undergoing surgery: individual changes over time and predictors of late cognitive functioning. *Neuro-oncology.* 2019;21(7):911-922.

17. van Kessel E, Emons MAC, Wajer IH, et al. Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a retrospective cohort study prior to antitumor treatment. *Neurooncol Pract.* 2019.

18. van Kessel E, Baumfalk AE, van Zandvoort MJE, Robe PA, Snijders TJ. Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a systematic review of neurocognitive functioning prior to anti-tumor treatment. *J Neurooncol.* 2017;134(1):9-18.

19. Cherkil S, Panikar D, Soman DK. Profiling Cognitive Deficits in Intra-Axial and Extra-Axial Tumors Using Addenbrooke's Cognitive Examination as a Screening Tool: An Indian Experience. *Asian J Neurosurg.* 2017;12(4):653-658.

20. Ozen LJ, Fernandes MA. Slowing Down after a Mild Traumatic Brain Injury: a strategy to improve cognitive task performance? *Arch Clin Neuropsych.* 2011;27(1):85-100.

21. Rijnen SJM, Meskal I, Emons WHM, et al. Evaluation of normative data of a widely used computerized neuropsychological battery: applicability and effects of sociodemographic variables in a Dutch sample. *Assessment.* 2017:1073191117727346.

22. Cosentino S, Stern Y. Consideration of cognitive reserve. In: Ravdin LD, Katzen HL, eds. *Handbook on the Neuropsychology of Aging and Dementia.* Cham: Springer International Publishing; 2019:11-23.

23. Stern Y. Cognitive reserve. *Neuropsychologia.* 2009;47(10):2015-2028.

24. Duffau H. Hodotopy, neuroplasticity and diffuse gliomas. *Neurochirurgie.* 2017;63(3):259-265.

25. Bernstein M. Under-recognized mental incapacity in brain tumour patients. *Nat Rev Neurol.* 2014;10(9):487-488.

26. Triebel KL, Martin RC, Nabors LB, Marson DC. Medical decision-making capacity in patients with malignant glioma. *Neurology.* 2009;73(24):2086.

27. Krogh J, Benros ME, Jørgensen MB, Vesterager L, Elfving B, Nordentoft M. The association between depressive symptoms, cognitive function, and inflammation in major depression. *Brain Beh Immunity.* 2014;35:70-76.

28. Brunoni AR, Lopes M, Fregni F. A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. *Int J Neuropsychopharm.* 2008;11(8):1169-1180.

29. Feil D, Razani J, Boone K, Lesser I. Apathy and cognitive performance in older adults with depression. *Int J Ger Psychiatry.* 2003;18(6):479-485.

30. Funes CM, Lavretsky H, Ercoli L, St Cyr N, Siddarth P. Apathy mediates cognitive difficulties in geriatric depression. *Am J Geriatr Psychiatry.* 2018;26(1):100-106.

31. Uher R, Payne JL, Pavlova B, Perlis RH. Major depressive disorder in DSM-5: implications for clinical practice and research of changes from DSM-IV. *Depr Anxiety.* 2014;31(6):459-471.

32. Keller AS, Leikauf JE, Holt-Gosselin B, Staveland BR, Williams LM. Paying attention to attention in depression. *Transl Psychiatry.* 2019;9(1):279.

33. Starkweather AR, Sherwood P, Lyon DE, McCain NL, Bovbjerg DH, Broaddus WC. A biobehavioral perspective on depressive symptoms in patients with cerebral astrocytoma. *J Neurosci Nurs.* 2011;43(1):17-28.

34. Noll KR, Sullaway CM, Wefel JS. Depressive symptoms and executive function in relation to survival in patients with glioblastoma. *J Neurooncol.* 2019;142(1):183-191.

35. Habets EJJ, Kloet A, Walchenbach R, Vecht CJ, Klein M, Taphoorn MJB. Tumour and surgery effects on cognitive functioning in high-grade glioma patients. *Acta Neurochir.* 2014;156(8):1451-1459.

36. Bommakanti K, Somayajula S, Suvarna A, et al. Pre-operative and post-operative cognitive deficits in patients with supratentorial meningiomas. *Clin Neurol Neurosurg.* 2016;143:150-158.

37. Habets EJ, Dirven L, Wiggenraad RG, et al. Neurocognitive functioning and health-related quality of life in patients treated with stereotactic radiotherapy for brain metastases: a prospective study. *Neuro-oncology.* 2016;18(3):435-444.

38. Dallabona M, Sarubbo S, Merler S, et al. Impact of mass effect, tumor location, age, and surgery on the cognitive outcome of patients with high-grade gliomas: a longitudinal study. *Neurooncol Pract.* 2017;4(4):229-240.

39. Tucha O, Smely C, Preier M, Lange KW. Cognitive deficits before treatment among patients with brain tumors. *Neurosurgery.* 2000;47(2):324-333; discussion 333-324.

40. Noll KR, Sullaway C, Ziu M, Weinberg JS, Wefel JS. Relationships between tumor grade and neurocognitive functioning in patients with glioma of the left temporal lobe prior to surgical resection. *Neuro-oncology.* 2015;17(4):580-587.

41. Miotto EC, Silva Junior A, Silva CC, et al. Cognitive impairments in patients with low grade gliomas and high grade gliomas. *Arq Neuro-Psiq.* 2011;69:596-601.

42. Gerritsen MJJ, Berg IJ, Deelman BG, Visser-Keizer AC, Jong BM-d. Speed of Information Processing After Unilateral Stroke. *J Cin Exp Neuropsych.* 2003;25(1):1-13.

43. Liouta E, Koutsarnakis C, Liakos F, Stranjalis G. Effects of intracranial meningioma location, size, and surgery on neurocognitive functions: a 3-year prospective study. *J Neurosurg.* 2016;124(6):1578-1584.

44. Koizumi H, Ideguchi M, Iwanaga H, et al. Cognitive dysfunction might be improved in association with recovered neuronal viability after intracranial meningioma resection. *Brain Res.* 2014;1574:50-59.

45. Tucha O, Smely C, Preier M, Becker G, Paul GM, Lange KW. Preoperative and postoperative cognitive functioning in patients with frontal meningiomas. *J Neurosurg.* 2003;98(1):21-31.

46. Friedman MA, Meyers CA, Sawaya R. Neuropsychological effects of third ventricle tumor surgery. *Neurosurgery.* 2008;62(suppl_3):791-798.

47. Meyers CA. Neurobehavioral functioning of adults with pituitary disease. *Psychother Psychosom.* 1998;67(3):168-172.

48. Correia N, Mullally S, Cooke G, et al. Evidence for a specific defect in hippocampal memory in overt and subclinical hypothyroidism. *The J Clin Endocrin Metab.* 2009;94(10):3789-3797.

49. de Kloet ER, Oitzl MS, Joëls M. Stress and cognition: are corticosteroids good or bad guys? *Trends Neurosci.* 1999;22(10):422-426.

8

50. Klein M, Engelberts NHJ, van der Ploeg HM, et al. Epilepsy in low-grade gliomas: The impact on cognitive function and quality of life. *Ann Neurol.* 2003;54(4):514-520.

51. González-Martínez J.A. NIM. Meningiomas and Epilepsy. In: J.H. L, ed. *Meningiomas.* London: Springer; 2009.

52. Rasmussen BK, Hansen S, Laursen RJ, et al. Epidemiology of glioma: clinical characteristics, symptoms, and predictors of glioma patients grade I–IV in the the Danish Neuro-Oncology Registry. *J Neurooncol.* 2017;135(3): 571-579.

53. van Lonkhuizen PJC, Rijnen SJM, van der Linden SD, Rutten GM, Gehring K, Sitskoorn MM. Subjective cognitive functioning in patients with a meningioma: Its course and association with objective cognitive functioning and psychological symptoms. *Psychooncol.* 2019;28(8):1654-1662.

54. Gehring K, Taphoorn MJB, Sitskoorn MM, Aaronson NK. Predictors of subjective versus objective cognitive functioning in patients with stable grades II and III glioma. *Neurooncol Pract.* 2015;2(1):20-31.

55. Hoofien D, Gilboa A, Vakil E, Barak O. Unawareness of Cognitive Deficits and Daily Functioning Among Persons With Traumatic Brain Injuries. *J Clin Exp Neuropsychol.* 2004;26(2):278-290.

56. Mahley RW. Apolipoprotein E: from cardiovascular disease to neurodegenerative disorders. *J Mol Med (Berl).* 2016;94(7):739-746.

57. Mahley RW, Huang Y. Apolipoprotein e sets the stage: response to injury triggers neuropathology. *Neuron.* 2012;76(5):871-885.

58. Tai L, Thomas R, Marottoli F, et al. The Role of APOE in Cerebrovascular Dysfunction. *Acta neuropathol.* 2016;131.

59. Teng Z, Guo Z, Zhong J, et al. ApoE Influences the Blood-Brain Barrier Through the NF-kappaB/MMP-9 Pathway After Traumatic Brain Injury. *Sci Rep.* 2017;7(1):6649.

60. Greenwood PM, Parasuraman R. Normal genetic variation, cognition, and aging. *Behav Cogn Neurosci Rev.* 2003;2(4):278-306.

61. Greenwood PM, Espeseth T, Lin M-K, Reinvang I, Parasuraman R. Longitudinal change in working memory as a function of APOE genotype in midlife and old age. *Scand J Psychol.* 2014;55(3):268-277.

62. Ahles TA, Saykin AJ, Noll WW, et al. The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. *Psycho-Oncology.* 2003;12(6):612-619.

63. Jochemsen HM, Muller M, van der Graaf Y, Geerlings MI. APOE ε4 differentially influences change in memory performance depending on age. The SMART-MR study. *Neurobiol of Aging.* 2012;33(4):832.e815-832.e822.

64. Ahles TA. Brain vulnerability to chemotherapy toxicities. *Psychooncol.* 2012;21(11):1141-1148.

65. Speidell AP, Demby T, Lee Y, et al. Development of a Human APOE Knock-in Mouse Model for Study of Cognitive Function After Cancer Chemotherapy. *Neurotox Res.* 2019;35(2):291-303.

66. Correa DD, Satagopan J, Baser RE, et al. APOE polymorphisms and cognitive functions in patients with brain tumors. *Neurology.* 2014;83(4):320.

67. Wefel JS, Deshmukh S, Brown PD, et al. Impact of apolipoprotein E (APOE) genotype on neurocognitive function (NCF) in patients with brain metastasis (BM): An analysis of NRG Oncology's RTOG 0614. *J Clin Oncol.* 2018;36(15_suppl):2065-2065.

68. Correa DD, Kryza-Lacombe M, Zhou X, et al. A pilot study of neuropsychological functions, APOE and amyloid imaging in patients with gliomas. *J Neurooncol.* 2018;136(3):613-622.

69. Correa DD, Satagopan J, Baser RE, et al. APOE polymorphisms and cognitive functions in patients with brain tumors. *Neurology.* 2014;83(4):320-327.

70. Correa DD, Satagopan J, Martin A, et al. Genetic variants and cognitive functions in patients with brain tumors. *Neuro-oncology.* 2019;21(10):1297-1309.

71. Villasana L, Acevedo S, Poage C, Raber J. Sex- and APOE Isoform-Dependent Effects of Radiation on Cognitive Function. *Radiat Res.* 2006;166(6):883-891.

72. Ahles TA, Li Y, McDonald BC, et al. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: the impact of APOE and smoking. *Psychooncol.* 2014;23(12):1382-1390.

73. Chambless LB, Kistka HM, Parker SL, Hassam-Malani L, McGirt MJ, Thompson RC. The relative value of postoperative versus preoperative Karnofsky Performance Scale scores as a predictor of survival after surgical resection of glioblastoma multiforme. *J Neurooncol.* 2015;121(2):359-364.

74. Lamborn KR, Chang SM, Prados MD. Prognostic factors for survival of patients with glioblastoma: recursive partitioning analysis. *Neuro-oncology.* 2004;6(3):227-235.

75. Ferrucci L, Koh C, Bandinelli S, Guralnik JM. Disability, functional status, and activities of daily living. In: Birren JE, ed. *Encyclopedia of Gerontology (Second Edition).* New York: Elsevier; 2007:427-436.

76. Johnson D, Wefel J. Relationship between cognitive function and prognosis in glioblastoma. *CNS oncol.* 2013;2:195-201.

77. Hilverda K, Bosma I, Heimans JJ, et al. Cognitive functioning in glioblastoma patients during radiotherapy and temozolomide treatment: initial findings. *J Neurooncol*. 2010;97(1):89-94.

78. Coomans MB, van der Linden SD, Gehring K, Taphoorn MJB. Treatment of cognitive deficits in brain tumour patients: current status and future directions. *Curr Opin Oncol.* 2019;31(6):540-547.

79. Johnson DR, Sawyer AM, Meyers CA, O'Neill BP, Wefel JS. Early measures of cognitive function predict survival in patients with newly diagnosed glioblastoma. *Neuro-oncology.* 2012;14(6):808-816.

80. Armstrong CL, Goldstein B, Shera D, Ledakis GE, Tallent EM. The predictive value of longitudinal neuropsychologic assessment in the early detection of brain tumor recurrence. *Cancer.* 2003;97(3):649-656.

81. Meyers CA, Hess KR. Multifaceted end points in brain tumor clinical trials: Cognitive deterioration precedes MRI progression. *Neuro-oncology.* 2003;5(2):89-95.

82. Arrieux J, Cole W, Ahrens A. A review of the validity of computerized neurocognitive assessment tools in mild traumatic brain injury assessment. *Concussion.* 2017;2:CNC31.

83. Vardy J, Wefel JS, Ahles T, Tannock IF, Schagen SB. Cancer and cancer-therapy related cognitive dysfunction: an international perspective from the Venice cognitive workshop. *Ann Oncol.* 2008;19(4):623-629.

84. Satoer D, Visch-Brink E, Dirven C, Vincent A. Glioma surgery in eloquent areas: can we preserve cognition? *Acta neurochir.* 2016;158(1):35-50.

85. Meskal I, Gehring K, van der Linden SD, Rutten G-JM, Sitskoorn MM. Cognitive improvement in meningioma patients after surgery: clinical relevance of computerized testing. *J Neurooncol.* 2015;121(3):617-625.

86. Reijneveld JC, Sitskoorn MM, Klein M, Nuyen J, Taphoorn MJB. Cognitive status and quality of life in patients with suspected versus proven low-grade gliomas. *Neurology.* 2001;56(5):618.

87. Butts AM, Weigand S, Brown PD, et al. Neurocognition in individuals with incidentally-identified meningioma. *J Neurooncol.* 2017;134(1):125-132.

88. Jean-Pierre P. Management of Cancer-related Cognitive Dysfunction-Conceptualization Challenges and Implications for Clinical Research and Practice. *US Oncol.* 2010;6:9-12.

89. Day J, Gillespie DC, Rooney AG, et al. Neurocognitive Deficits and Neurocognitive Rehabilitation in Adult Brain Tumors. *Curr Treat Opt Neurol.* 2016;18(5):22.

90. Jammeh EA, Carroll CB, Pearson SW, et al. Machine-learning based identification of undiagnosed dementia in primary care: a feasibility study. *BJGP Open.* 2018;2(2): bjgpopen18X101589.

91. Krupp W, Klein C, Koschny R, Holland H, Seifert V, Meixensberger J. Assessment of neuropsychological parameters and quality of life to evaluate outcome in patients with surgically treated supratentorial meningiomas. *Neurosurgery.* 2009;64(1):40-47.

92. van den Bent MJ, Wefel JS, Schiff D, et al. Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. *Lancet Oncol.* 2011;12(6):583-593.

93. Anderson SW, Damasio H, Tranel D. Neuropsychological impairments associated with lesions caused by tumor or stroke. *Arch Neurology.* 1990;47(4):397-405.

94. Elgamal SA, Roy EA, Sharratt MT. Age and verbal fluency: the mediating effect of speed of processing. *Can Geriatr J.* 2011;14(3):66-72.

95. Rijnen SJM, Butterbrod E, Rutten G-JM, Sitskoorn MM, Gehring K. Presurgical Identification of Patients With Glioblastoma at Risk for Cognitive Impairment at 3-Month Follow-up. *Neurosurgery.* 2020. doi: 10.1093/neuros/nyaa190

96. Zarino B, Di Cristofori A, Fornara GA, et al. Long-term follow-up of neuropsychological functions in patients with high grade gliomas: can cognitive status predict patient's outcome after surgery? *Acta Neurochir.* 2020;162(4):803-812.

97. Gehring K, Stuiver MM, Visser E, et al. A pilot randomized controlled trial of exercise to improve cognitive performance in patients with stable glioma: a proof of concept. *Neuro-oncology.* 2020;22(1):103-115.

98. Chen X, Maguire B, Brodaty H, O'Leary F. Dietary Patterns and Cognitive Health in Older Adults: A Systematic Review. *J Alzheimer's Dis.* 2019;67:583-619.

99. Wang C, Chan JSY, Ren L, Yan JH. Obesity Reduces Cognitive and Motor Functions across the Lifespan. *Neural Plast.* 2016;2016:2473081-2473081.

100. Senders JT, Zaki MM, Karhade AV, et al. An introduction and overview of machine learning in neurosurgical care. *Acta Neurochir.* 2018;160(1):29-38.

APPENDICES

APPENDIX I

Summary in Dutch

Discussie van de bevindingen in dit proefschrift en aanbevelingen voor onderzoek en klinische praktijk

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AANLEIDING VOOR HET ONDERZOEK

Primaire hersentumoren zijn tumoren die ontstaan uit het hersenweefsel, zoals gliaweefsel, hypofyseweefsel of de hersenvliezen. Primaire hersentumoren zeldzaam,[1] maar zorgen voor een relatief grote druk op de gezondheidszorg.[2] Een van de redenen hiervoor is de intensieve, multidisciplinaire behandeling die de patiënten ondergaan. Daarnaast spelen de significante lichamelijke en psychologische morbiditeit die gepaard gaat met aanwezigheid en behandeling van een hersentumor een rol.

Verstoring van cognitief functioneren is een van de meest voorkomende symptomen is bij patiënten met zowel goedaardige als kwaadaardige hersentumoren. Een cognitieve stoornis is geen geïsoleerd symptoom; het kan een negatieve uitwerking kan hebben op dagelijks functioneren van patiënten, bijvoorbeeld op werk,[3,4] op kwaliteit van leven[5] en zelfs bekwaamheid voor medische besluitvorming.[6,7] Echter worden cognitieve stoornissen veelal niet herkend in de kliniek, onder andere omdat ze moeilijk op te merken zijn in korte consulten en doorgaans geen prioriteit zijn in de spreekkamer.[8] Tenslotte is monitoring van cognitief functioneren met neuropsychologische tests vaak geen onderdeel van de standaard zorg.[9]

Om het belang van neuropsychologisch onderzoek als onderdeel van de zorg voor patiënten met hersentumoren te onderbouwen, werden de volgende doelen binnen dit proefschrift opgesteld:

1) Bijdragen aan onze kennis over en begrip van cognitieve problematiek bij patiënten met primaire hersentumoren die chirurgische behandeling ondergaan,
2) De waarde van postoperatieve metingen van cognitief functioneren voor prognostische doeleinden (i.e., het voorspellen van ziekte uitkomsten) illustreren,
3) De aansluiting tussen wetenschappelijk onderzoek en vragen en behoeften in de klinische praktijk te verbeteren door gebruik van klinisch intuïtieve onderzoeksmethoden.

De studies in dit proefschrift zijn gericht op patiënten die een operatie ondergingen voor een primaire hersentumor bij de afdeling Neurochirurgie van het Elisabeth-Tweesteden Ziekenhuis, Tilburg.

In het *eerste deel* van het proefschrift onderzochten we de prevalentie van en patronen in cognitieve stoornissen in patiënten met een niet-functionerend hypofyse adenoom (**Hoofdstuk 2**), glioom (**Hoofdstuk 4**) en meningeoom (**Hoofdstuk 5**) vóór en drie maanden na operatie. Daarbij werd ook gekeken naar welke patiënt- en ziektekenmerken van belang zijn in de voorspelling van cognitie. In Hoofdstuk 3 werd specifiek gekeken naar de invloed van dragerschap van het APOE-ε4 allel op cognitief functioneren tot 12 maanden na operatie (**Hoofdstuk 3**) bij patiënten met een meningeoom of glioom.

In het *tweede deel* van het proefschrift onderzochten we de waarde van cognitieve maten voor verschillende prognostische doeleinden. **Hoofdstuk 6** illustreert een onderzoek naar de vraag of cognitieve verstoring tijdens vroege fase van adjuvante behandeling gerelateerd is aan een kortere overlevingsduur bij patiënten met een glioblastoom. **Hoofdstuk 7** beschrijft een longitudinale studie waarbij onderzocht werd of cognitieve achteruitgang op een gepersonaliseerde set neuropsychologische testen radiologische groei van een hooggradig glioom (anaplastisch astrocytoom of glioblastoom) kan voorspellen.

Discussie van de bevindingen

Prevalentie en verloop van cognitieve problemen voor en na behandeling

De resultaten van onze onderzoeken illustreren dat patiënten met een primaire hersentumor significant risico lopen op cognitieve verstoringen. Vóór operatie toonde 56% van patiënten met een niet-functionerend hypofyse adenoom (NFHA, **Hoofdstuk 2**) een stoornis op minstens één cognitief domein. 57% en 55% van de patiënten met respectievelijk een meningeoom (**Hoofdstuk 5**) of glioom (**Hoofdstuk 4**) toonde een cognitief profiel dat gekenmerkt werd door de aanwezigheid van een stoornis op minstens één cognitieve functie. Aangenomen wordt dat cognitieve problematiek milder is in goedaardige tumoren, zoals meningeomen, dan in kwaadaardige tumoren, zoals gliomen.[10] Onze resultaten duiden er juist op dat stoornissen in gelijke mate kunnen voorkomen vóór start van behandeling.

In tegenstelling tot de algemene verwachting dat verwijdering van een (goedaardige) tumor leidt tot cognitieve verbetering, was de prevalentie van cognitieve stoornissen drie maanden na operatie niet significant gedaald ten opzichte van het preoperatieve meetmoment; 63% van NFHA patiënten en 45% van meningeoom patiënten toonde nog één of meerdere cognitieve stoornissen. In glioblastoom patiënten (**Hoofdstuk 6**), de meest kwaadaardige vorm van een glioom, was de prevalentie drie maanden na operatie zelfs 87%.

Onze resultaten bevestigen daarnaast ook eerder onderzoek[11] dat aantoont dat de keuze voor analyses op groepsniveau (gebruik van gemiddelde scores van de steekproef) of patiëntniveau (gebruik van individuele scores per patiënt) de resultaten, en daarmee de boodschap van wetenschappelijk onderzoek kunnen beïnvloeden.

In **Hoofdstuk 2** vonden wij bijvoorbeeld dat patiënten met NFHA als groep stabiele cognitieve prestaties op de testen leverden over de tijd (geen significante verandering in het groepsgemiddelde). Echter viel op dat er 28% van de individuele patiënten klinisch relevante vooruitgang lieten zien, gemeten met de Reliable Change Index.[12] Nog eens 28% van de patiënten toonde klinische relevante achteruitgang. In deze groep patiënten maskeerde dus het resultaat op groepsniveau de uiteenlopende trajecten die individuele patiënten lieten zien. Clinici moeten dus voorzichtig zijn met het vertalen van groepsresultaten naar patiënten die gezien worden in de praktijk.

Welke cognitieve profielen bestaan?

De vraag *welke* cognitieve functies (het meest) aangedaan zijn kan op verschillende manieren onderzocht worden. In voorgaande studies werden verschillende cognitieve functies telkens apart onderzocht en voorspeld. Echter negeert deze aanpak een belangrijk aspect van cognitieve functies – en daarmee ook van cognitieve stoornissen – , namelijk dat cognitieve functies onderlinge samenhang tonen, omdat zij deels op dezelfde mechanismen berusten.[13,14] Een ‘basisfunctie’ als verwerkingssnelheid is bijvoorbeeld belangrijk voor complexere functies, zoals het vermogen om te schakelen tussen opdrachten. In **Hoofdstuk 4** (gliomen) en **5** (meningeomen) pasten wij Latente Klassen Analyse (LCA) toe om patronen te onderzoeken in prestaties over verschillende cognitieve testen heen, waarbij onderlinge samenhang tussen functies in acht genomen kan worden. Met behulp van deze analysemethode vonden wij verschillende “stoornisprofielen”. De pre-operatieve profielen gevonden in glioom- en meningeoompatiënten zijn weergegeven in Figuur 1.

Voor operatie

Twee stoornisprofielen kwamen voor in beide diagnosen; een *intact* profiel (lage kansen op stoornissen op alle cognitieve testen) en een *globaal verstoord* profiel (hoge kansen op stoornissen op alle cognitieve testen). Deze profielen lijken twee uiteinden van het cognitieve spectrum te illustreren. De andere profielen leken meer specifiek voor meningeoompatiënten (een profiel met verstoring van *executieve functies en verwerkingssnelheid* en een profiel met verstoring *van psychomotorische en executieve functies*) of voor glioompatiënten (een profiel met geïsoleerde verstoring van *executieve functies*, een profiel met geïsoleerde verstoring van *visuele en verbale geheugenfuncties* en een profiel met stoornissen op *verschillende domeinen die snelheid gerelateerd lijken*).

Na operatie

In **Hoofdstuk 5** werden ook postoperatieve cognitieve-stoornisprofielen binnen de groep patiënten met een meningeoom. Ook na operatie kwam een *intact* profiel naar voren. De andere profielen die op dit meetmoment gevonden werden zagen er anders uit dan vóór operatie; een profiel met geïsoleerde verstoring van *verbaal geheugen*, een profiel met verstoring van *executieve, verwerkingssnelheid én psychomotorische functies*, een profiel met verstoring van *psychomotorische en aandachtsfuncties* en een profiel met *diffuse verstoring*, waarbij simpele motoriek en visueel geheugen relatief bespaard bleven.

Bij het vergelijken van de pre- en postoperatieve profielen viel op dat er een groep patiënten *herstel* liet zien; zij gingen bijvoorbeeld van een verstoord profiel naar het intacte profiel. Daarnaast was er een groep patiënten die juist *verslechtering* liet zien; bijvoorbeeld een overgang van het intacte profiel naar een verstoord profiel. Tenslotte was een belangrijke bevinding dat een aantal patiënten een *kwalitatief ander profiel* liet zien na operatie; zij gingen bijvoorbeeld van een *psychomotorisch-executief* profiel naar een *geheugen* profiel.

Uit deze resultaten concluderen wij dat de cognitieve problematiek na operatie, en daarmee wellicht problemen in dagelijks functioneren, anders kunnen zijn dan voor operatie. In het volgen van cognitie over de tijd moeten onderzoekers en clinici zich ervan bewust zijn dat, naast vooruitgang en achteruitgang, er ook *kwalitatieve veranderingen* op kunnen treden in cognitie.

Welke factoren zijn relevant in het voorspellen van cognitie?

De bevindingen van Hoofdstukken 2-5 bevestigen dat factoren op zowel patiënt- als ziekteniveau cognitie van patiënten met primaire hersentumoren kunnen beïnvloeden. Een belangrijk inzicht uit onze LCA studies is dat er factoren zijn die lijken te onderscheiden tussen intact versus verstoord cognitief functioneren, terwijl andere factoren meer lijken te onderscheiden tussen verschillende verstoringen.

Patiëntkenmerken

Scores op de neuropsychologische testen waren gecontroleerd voor effecten van leeftijd, opleidingsniveau en geslacht, die in de gezonde populatie zijn aangetoond.[15,16] Resultaten van **Hoofdstuk 4** (gliomen) en **5** (meningeomen) tonen aan dat leeftijd en opleidingsniveau nog additionele effecten hebben op cognitie bij hersentumorpatiënten, waarbij jongere leeftijd en hoog opleidingsniveau voorspellend waren voor een intact cognitief profiel. In **Hoofdstuk 5** werd gevonden dat meningeoompatiënten met een intact cognitief profiel na operatie een significant lagere score toonden op een zelfrapportagelijst voor depressie symptomatologie dan patiënten met verstoorde cognitieve profielen.

<u>Stemming en sociodemografische informatie zijn relatief eenvoudig te verzamelen in het kader van reguliere zorg en kan een snelle indicatie geven van de kans dat een patiënt een intact cognitief profiel heeft.</u>

Tumorkenmerken

Verschillende tumorkenmerken hingen samen met cognitief functioneren, met name vóór operatie. Een lager tumorvolume hing samen met een intact cognitief profiel in meningeoom- én glioompatiënten. Dit kan verklaard worden door minder schade aan en/of verdrukking van het hersenweefsel. Eenzelfde effect werd gevonden voor de tumorgraad, waarbij laaggradige gliomen vaker voorkwamen bij patiënten met het intacte profiel. Deze bevinding past in het beeld dat laaggradige gliomen minder schade veroorzaken en meer ruimte laten voor functionele reorganisatie in het brein.[17] De locatie van de tumor lijkt met name juist onderscheid te *maken tussen verstoorde profielen* (bilaterale lokalisatie bij meningeomen hing bijvoorbeeld samen met het "*executief-snelheid*" profiel, infiltratie van de frontaalkwab bij gliomen hing samen met het "*globaal verstoord*" profiel). In **Hoofdstuk 2** kwam naar voren dat uitval van de hypofyse-bijnier as (cortisol) en/of hypofyse-schildklier as (schildklierhormoon) samenhing met een beter verbaal geheugen in patiënten met een niet-functionerend hypofyse adenoom. Dit effect kan wellicht verklaard worden doordat patiënten met uitval suppletie ontvingen ten tijde van de neuropsychologische testen. Suprasellaire groei gemeten met de Hardy-Wilson categorisatie was niet gerelateerd aan cognitieve prestaties, wat erop kan duiden dat deze klinisch gebruikte methode niet sensitief genoeg is om cognitie te voorspellen.

Tumorkenmerken worden veelal verzameld als onderdeel van reguliere zorg. Sommige kenmerken lijken informatie geven over de kans op een intact cognitief profiel, terwijl andere lijken te onderscheiden tussen verschillende verstoringen.

Vroege symptomen

Gebruik van anti-epileptica vóór operatie hing samen met een intact cognitief profiel bij glioompatiënten. Enerzijds is dit in contradictie met eerder onderzoek dat juist slechtere prestaties vindt bij patiënten die deze medicatie gebruiken.[18,19] Anderzijds is epilepsie, en dus anti-epilepticagebruik, indicatief voor een laaggradige tumor. Bij meningeomen was anti-epileptica gebruik juist voorspellend voor een *psychomotorisch-executief* profiel. Meningeoompatiënten die geen cognitieve klachten rapporteerden ten tijde van de diagnose hadden een hogere kans op een intact cognitief profiel. Bij glioompatiënten vonden wij geen effect van deze factor.

Symptomatologie is bekend ten tijde van vroege diagnostiek. De relatie met cognitie kan verschillend zijn van voor verschillende typen tumoren.

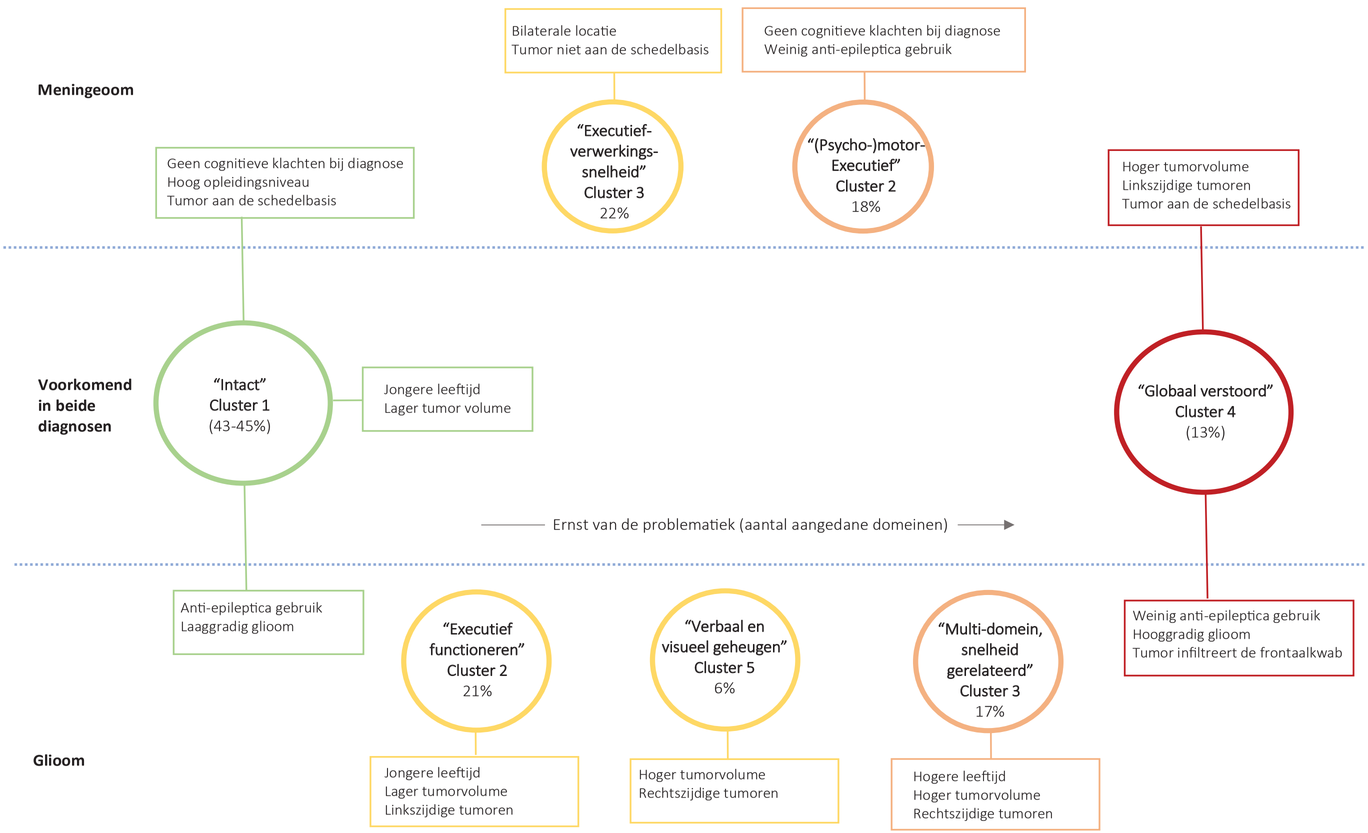
Dragerschap van het APOE ε4 allel

Het polymorfe gen APOE codeert voor apolipoproteine E (ApoE). Dit glycoproteïne is betrokken bij processen die belangrijk zijn voor herstel en plasticiteit in het centrale zenuwstelsel. Eerder onderzoek toont aan dat ApoE4, dat tot uiting komt door dragerschap van het APOE ε4 allel, minder effectief herstel bevorderd dan andere vormen van ApoE en zelfs schadelijke reacties kan oproepen bij letsel in het brein.[20] Deze effecten lijken te kunnen doorwerken in cognitief functioneren van o.a. patiënten met ischemische beroerte en kanker buiten het centrale zenuwstelsel.[21,22] Bij hersentumorpatiënten is echter beperkt onderzoek gedaan naar de potentiële negatieve effecten van APOE op cognitie, en concentreren studies zich op reeds behandelde patiënten met kwaadaardige tumoren.[23-25]

In onze prospectieve longitudinale studie met glioom- en meningeoompatiënten vonden wij géén effect van APOE ε4 allel dragerschap op cognitieve prestaties vóór start van behandeling. Onze hypothese is dat bij relatief traag groeiende hersentumoren kans is voor het brein om toch aan te passen aan de schadelijke effecten van ApoE4. Het kan zijn dat er wel afwijkende activatiepatronen bestaan in ε4 dragers in vergelijking met niet-dragers.[26] Dit zou met functionele beeldvorming (fMRI) kunnen worden bestudeerd.

In tegenstelling tot eerder gepubliceerd onderzoek bij glioompatiënten die (> 4 jaar geleden) chirurgische en adjuvante behandeling hadden ondergaan,[24] vonden wij geen negatief effect van APOE ε4 allel dragerschap op het beloop van cognitie functioneren van onze patiënten over de tijd (tot 3 en 12 maanden na operatie). Hiervoor zijn een aantal methodologische verklaringen, waaronder het feit dat onze studie cognitieve meting tijdens en kort na adjuvante behandeling plaatsvonden. De schadelijke effecten van chemo- en radiotherapie kunnen na dit tijdstip nog doorwerken.[27,28] Het kan dus zijn dat de effecten van APOE op cognitie ook pas later manifesteren. Daarnaast kan het ook zo zijn dat de effecten zich vooral bij bepaalde groepen manifesteren. Vervolgstudies zouden daarom in grote steekproeven kunnen stratificeren voor potentiële moderatoren, zoals geslacht, leeftijd en andere genetische kenmerken.[29-31]

Studie naar genetische determinanten van cognitie in hersentumorpatiënten is momenteel nog beperkt. Alhoewel onze studie geen effect van APOE ε4 dragerschap aantoonde, is meer onderzoek naar dit en andere genetische kenmerken relevant om (late) cognitieve uitkomsten bij deze populatie te voorspellen.



Figuur 1. Weergave van preoperatieve cognitieve profielen bij patiënten met een meningeoom en glioom (in de cirkels) en samenhangende patiënt- en ziektekenmerken (in de vierkanten).

De prognostische waarde van cognitieve data in zorg voor patiënten met een hooggradig glioom

Verschillende tumor-specifieke (bijvoorbeeld maligniteit) en patiënt-specifieke kenmerken (bijvoorbeeld functionele status en leeftijd) kunnen informatie verschaffen over het gedrag van de tumor en de prognose van patiënten.[32,33] Cognitieve prestaties - en veranderingen daarin - worden steeds meer onderzocht als aanvullende marker van tumoractiviteit, omdat prestaties onder invloed staan van bijvoorbeeld infiltratieve groei, druk op omliggend hersenweefsel en reactief oedeem.[34] Vroege metingen van cognitieve prestaties lijken aanvullende informatie te kunnen geven over bijvoorbeeld overlevingsduur, onafhankelijk van de eerder genoemde kenmerken.[34] In **Hoofdstuk 6** en **7** sluiten aan bij twee vragen die momenteel open staan in het onderzoek naar het gebruik van klinisch verkregen cognitieve metingen in het voorspellen van ziekte uitkomsten, namelijk 1) voor welk(e) prognostisch doeleinde(n) cognitieve metingen gebruikt kunnen worden, en 2) hoe we cognitie dienen te meten als het gebruikt wordt als voorspellende factor in plaats van een uitkomst.

In **Hoofdstuk 6** onderzochten we op de vraag of stoornissen in de vroege adjuvante behandelfase, gemeten op één afspraak als onderdeel van reguliere klinische follow-up, kunnen worden gebruikt voor vroege prognostische stratificatie van glioblastoom patiënten. Hiervoor gebruikte wij het, in medisch onderzoek relatief onbekende, Accelerated Failure Time model, dat het effect van een risicofactor kan vertalen in een verschil in overlevingsduur. Onze resultaten toonden aan dat patiënten met een stoornis op testen van executief functioneren (Stroop test deel III) en reactiesnelheid (Stroop test deel I) ongeveer 25% kortere overlevingstijd hadden dan patiënten zonder dergelijke stoornissen, zelfs na het controleren voor klinische kenmerken en extra behandeling na ziekteprogressie.

<u>Verstoring in prestatie op slechts cognitieve twee testen, gemeten bij een regulier zorgmoment 3 maanden na operatie, is een eenvoudig te verkrijgen maat die clinici al op een vroeg moment kan informeren relatieve verschillen in overlevingsduur van patiënten.</u>

Hoofdstuk 7 beschrijft een studie waarbij onderzocht werd of verandering in het cognitief functioneren over de tijd als aanvullende marker gebruikt kan worden om groei van een hooggradig glioom te voorspellen. In deze studie werd cognitie driemaandelijks gemeten op dezelfde dag als de MRI scan die in de reguliere zorg gebruikt wordt en gouden standaard geldt om tumorgroei te monitoren. Uniek in deze studie is dat voor iedere patiënt een gepersonaliseerde selectie gemaakt werd van 3 tests waarop zij gemonitord werden. Deze selectie werd gebaseerd op de functies waarop patiënten direct na verwijdering van de tumor het meest op vooruitgingen. Onze hypothese was dat de functies die het meest herstellen als de tumor verwijderd, ook het snelst achteruitgaan als de tumor terugkeert.

In 25 patiënten met een anaplastich astrocytoom of glioblastoom vonden wij dat cognitieve achteruitgang (een achteruitgang op 2 van de 3 gepersonaliseerde testen gemeten met de eerder genoemde Reliable Change Index) vastgesteld werd ten tijde van of zelfs vóór groei van de tumor vastgesteld op de MRI scan in 60% van de patiënten. Patiënten waarbij de tumor stabiel bleef, bleven ook overwegend cognitief stabiel (80% geen achteruitgang). De kans van tumorgroei op de MRI scan was 5 keer hoger in patiënten die cognitieve achteruitgang toonden op hun testen dan in patiënten die stabiel waren.

Veranderingen in prestaties op een korte, gepersonaliseerde set cognitieve testen kunnen een aanvullende rol spelen in het monitoren en op tijd herkennen van tumorprogressie na behandeling.

Concluderend, meting van cognitief functioneren:

1) kan zowel *in een vroeg stadium prognostische informatie geven* ("welke patiënten hebben risico op kortere overleving?") als *over de tijd heen aanvullende informatie geven over terugkeer van de tumor* ("welke patiënten hebben op korte termijn een groter risico op ziekteprogressie?"),

2) kan gedaan worden met *korte, gerichte testprotocollen* (met een uniforme of gepersonaliseerde testselectie) op reguliere zorgmomenten. Hierdoor blijft de druk op kwetsbare patiënten en het zorgtraject beperkt.

Uitdagingen en kansen voor de (aansluiting tussen) klinische praktijk en onderzoek

Het is belangrijk dat in wetenschappelijk onderzoek kritisch geëvalueerd wordt in hoeverre de gebruikte methodologie aansluit bij wat clinici willen weten en, daaraan gerelateerd, of de resultaten die voortkomen uit de methodologie klinisch intuïtief gerapporteerd (kunnen) worden.

Voor het voorspellen van de prognose van een patiënt met een ongeneeslijke hersentumor is het voor een clinicus bijvoorbeeld relevanter om te weten hoe een karakteristiek, zoals een vroege cognitieve stoornis, samenhangt met de *overlevingsduur* dan met *de kans op overlijden*. Doorgaans worden echter nog methoden toegepast die juist het laatste rapporteren. **Hoofdstuk 6** toont aan dat het Accelerated Failure Time framework een klinisch intuïtief alternatief kan bieden aan reguliere methoden in overlevingsstudies. Een methode die cognitieve profielen opspoort in data, zoals LCA uit **Hoofdstuk 4 en 5**, geeft niet alleen een natuurgetrouwer beeld van cognitief functioneren dan het apart onderzoeken van cognitieve domeinen, het sluit ook beter aan bij de manier waarop klinisch neuropsychologen in de praktijk bij een individuele patiënt evalueren welke sterktes en zwaktes aanwezig zijn waarop ingespeeld kan worden.

Voor clinici is het belangrijk om bewust te zijn dat cognitieve stoornissen veel voorkomen én verschillende facetten van functioneren van patiënten kunnen beïnvloeden. Echter heeft de aanwezigheid van en het type cognitieve stoornissen ook uitwerking op verschillende aspecten van het werk van clinici. De aanwezigheid van geheugenproblematiek zal bijvoorbeeld andere eisen stellen aan de consultvoering dan de aanwezigheid van globale cognitieve verstoring of problematiek met mentaal tempo. Daarnaast hebben cognitieve stoornissen invloed op de capaciteit voor besluitvorming. Aangezien het patiëntperspectief steeds groter belang krijgt in besluitvorming rondom neurochirurgische behandeling, zal dit laatste aspect meer aandacht vragen in zowel onderzoek als praktijk.

De manier waarop cognitie getest dient te worden behoeft in de toekomst meer aandacht. Vanuit internationale werkgroepen, waaronder de Response Assessment in Neuro-Oncology group, is een consensus geformuleerd over een set van cognitieve functies die in patiënten met hersentumoren onderzocht dient te worden.[35] Echter behoeft de inhoud van neuropsychologisch onderzoek enige flexibiliteit, bijvoorbeeld op basis van het doel dat gediend wordt. Bij het meten van *cognitie als uitkomstmaat*, tonen onze studies aan dat een brede evaluatie vóór en na operatie van belang is, omdat uiteenlopende problematiek gevonden kan worden. Door breed te testen kan een zo volledig mogelijk beeld verkregen worden van sterktes en zwaktes van patiënten, en veranderingen daarin over de tijd. Een testbatterij kan hierbij ook aangepast worden op o.a. de locatie van de tumor, bijvoorbeeld extra testen van executief functioneren bij een tumor in de frontaalkwab. Bij het meten van *cognitie als voorspeller van ziekte* uitkomsten, volstaat juist wellicht een beperkter, maar gerichter, neuropsychologisch onderzoek. De inhoud van het onderzoek kan hier per patiënt helemaal verschillen.

Uit dit proefschrift komen enkele potentiële richtingen voor toekomstig wetenschappelijk onderzoek naar voren. Een van deze richtingen leidt naar de verkenning van factoren die beschermend lijken te werken voor cognitief functioneren. Uit ons onderzoek kwamen een aantal patiënt- en ziektekenmerken naar voren die samenhingen met een intact profiel. Echter waren dit overwegend statische factoren, zoals leeftijd en opleidingsniveau. *Dynamische predictoren* van intact cognitief functioneren kunnen handvatten bieden voor verbetering cognitie van patiënten die aanvankelijk een verstoord profiel tonen. In ons onderzoek kon bijvoorbeeld depressieve symptomatologie een onderscheid tussen het intacte en de verstoorde profielen. Eerder is ook aangetoond dat, bijvoorbeeld fysieke activiteit tot verbetering kan leiden in verschillende cognitieve functies.[36]

Om beter aan te sluiten bij de kliniek moet in wetenschappelijk onderzoek ook rekening gehouden worden met het feit dat er, naast verslechtering en verbetering van cognitief functioneren, ook kwalitatieve veranderingen kunnen optreden die niet in een van die twee categorieën vallen. Deze kwalitatieve veranderingen kunnen niet eenvoudig met traditionele statistiek onderzocht worden. Daarom is het van belang dat meer complexe statistische methoden, waaronder machine learning, betrokken worden in onderzoek naar cognitie bij hersentumor patiënten. Momenteel wordt in het Elisabeth-Tweesteden ziekenhuis als onderdeel van Topklinische Zorg en Onderzoek 2020-2024 (TZO) projecten (zie: https://www.etz.nl/Over-ETZ/Thema/TZO) gewerkt aan de ontwikkeling van een classificatie tool die op basis van aangevoerde data predicties kan doen over cognitieve uitkomsten voor individuele patiënten.

CONCLUSIE

Verstoring van cognitief functioneren is een veelvoorkomend symptoom van primaire hersentumoren. Verstoringen blijven na behandeling even prevalent op groepsniveau, maar kunnen een kwalitatief andere uiting hebben in de individuele patiënt. Patiënt- en ziektekarakteristieken dragen bij aan specifieke cognitieve stoornissen, terwijl de invloed van variatie in APOE allel dragerschap wellicht beperkt is. Kort, gericht neuropsychologisch onderzoek na operatie kan helpen bij zowel vroege prognostische verfijning als bij monitoring van de ziekte over tijd. We stellen voor om het framework voor onderzoek naar cognitie op meerdere manieren te verbreden; 1) van onderzoek van prestaties op aparte testen naar onderzoek van profielen, die prestaties op verschillende tests combineren, 2) van “verbetering, stabiliteit en verslechtering” van prestaties naar “kwalitatieve veranderingen” in cognitie over de tijd, en 3) van (secundaire) uitkomstmaat naar een maat met een veelzijdige toegevoegde waarde. Mogelijkheden voor toekomstig onderzoek kunnen liggen in het gebruik van geavanceerde, data-driven analyses die gericht zijn op het leveren van bruikbare (classificatie) instrumenten voor de klinische praktijk.

REFERENTIES

1. Ostrom QT, Cioffi G, Gittleman H, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012–2016. *Neuro-oncology.* 2019;21(Supplement_5):v1-v100.
2. Bayen E, Laigle-Donadey F, Prouté M, Hoang-Xuan K, Joël M-E, Delattre J-Y. The multidimensional burden of informal caregivers in primary malignant brain tumor. *Supp Care Cancer.* 2017;25(1):245-253.
3. Nugent BD, Weimer J, Choi CJ, et al. Work productivity and neuropsychological function in persons with skull base tumors. *Neuro-Oncology Pract.* 2014;1(3):106-113.
4. Duijts SFA, van der Beek AJ, Boelhouwer IG, Schagen SB. Cancer-related cognitive impairment and patients' ability to work: a current perspective. *Curr Op Supp Pall Care.* 2017;11(1).
5. Klein M, Taphoorn MJB, Heimans JJ, et al. Neurobehavioral Status and Health-Related Quality of Life in Newly Diagnosed High-Grade Glioma Patients. *J Clin Oncol.* 2001;19(20):4037-4047.
6. Bernstein M. Under-recognized mental incapacity in brain tumour patients. *Nat Rev Neurol.* 2014;10(9):487-488.
7. Lee J, Hall RCW. The Impact of Gliomas on Cognition and Capacity. *J Am Acad Psych Law Online.* 2019:JAAPL.003841-003819.
8. Day J, Gillespie DC, Rooney AG, et al. Neurocognitive Deficits and Neurocognitive Rehabilitation in Adult Brain Tumors. *Curr Treat Opt Neurol.* 2016;18(5):22.
9. Talacchi A, Santini B, Savazzi S, Gerosa M. Cognitive effects of tumour and surgical treatment in glioma patients. *J Neurooncol.* 2011;103(3):541-549.
10. Meskal I, Gehring K, Rutten G-JM, Sitskoorn MM. Cognitive functioning in meningioma patients: a systematic review. *J Neurooncol.* 2016;128(2):195-205.
11. van Loenen IS, Rijnen SJM, Bruijn J, Rutten GM, Gehring K, Sitskoorn MM. Group Changes in Cognitive Performance After Surgery Mask Changes in Individual Patients with Glioblastoma. *World Neurosurg.* 2018;117:e172-e179.
12. Maassen GH, Bossema E, Brand N. Reliable change and practice effects: outcomes of various indices compared. *J Clin Exp Neuropsych.* 2009;31(3):339-352.
13. Drew MA, Starkey NJ, Isler RB. Examining the Link between Information Processing Speed and Executive Functioning in Multiple Sclerosis. *Arch Clin Neuropsych.* 2009;24(1):47-58.
14. Geng J, Schnur TT, Janssen N. Relative speed of processing affects interference in Stroop and picture–word interference paradigms: evidence from the distractor frequency effect. *Lang Cog Neurosci.* 2014;29(9):1100-1114.
15. Rijnen SJM VDLS, Emons WHM, Sitskoorn MM, Gehring K. . Test-retest reliability and practice effects of the computerized neuropsychological test battery CNS Vital Signs: A solution-oriented approach. *Psychol Assess.* 2018;In press.
16. Rijnen SJ, Meskal I, Emons WH, et al. Evaluation of normative data of a widely used computerized neuropsychological battery: Applicability and effects of sociodemographic variables in a Dutch sample. *Assessment.* 2017:1073191117727346.
17. Duffau H. Hodotopy, neuroplasticity and diffuse gliomas. *Neurochirurgie.* 2017;63(3):259-265.

18. Dijkstra M, van Nieuwenhuizen D, Stalpers LJA, et al. Late neurocognitive sequelae in patients with WHO grade I meningioma. *J Neurol Neurosurg Psych.* 2009;80(8):910.

19. Klein M, Engelberts NHJ, van der Ploeg HM, et al. Epilepsy in low-grade gliomas: The impact on cognitive function and quality of life. *Ann Neurol.* 2003;54(4):514-520.

20. Mahley RW, Huang Y. Apolipoprotein e sets the stage: response to injury triggers neuropathology. *Neuron.* 2012;76(5):871-885.

21. Ahles TA, Saykin AJ, Noll WW, et al. The relationship of APOE genotype to neuropsychological performance in long-term cancer survivors treated with standard dose chemotherapy. *Psycho-Oncol.* 2003;12(6):612-619.

22. Ballard CG, Morris CM, Rao H, et al. APOEε4 and cognitive decline in older stroke patients with early cognitive impairment. *Neurology.* 2004;63(8):1399-1402.

23. Correa D, DeAngelis L, Shi W, Thaler H, Lin M, Abrey L. Cognitive functions in low-grade gliomas: Disease and treatment effects. *J Neurooncol.* 2007;81:175-184.

24. Correa DD, Kryza-Lacombe M, Zhou X, et al. A pilot study of neuropsychological functions, APOE and amyloid imaging in patients with gliomas. *J Neurooncol.* 2018;136(3):613-622.

25. Correa DD, Satagopan J, Baser RE, et al. APOE polymorphisms and cognitive functions in patients with brain tumors. *Neurology.* 2014;83(4):320-327.

26. Jochemsen HM, Muller M, van der Graaf Y, Geerlings MI. APOE ε4 differentially influences change in memory performance depending on age. The SMART-MR study. *Neurobiol Aging.* 2012;33(4):832.e815-832.e822.

27. Balentova S, Adamkov M. Molecular, Cellular and Functional Effects of Radiation-Induced Brain Injury: A Review. *Int J Mol Sci.* 2015;16(11):27796-27815.

28. Brown WR, Blair RM, Moody DM, et al. Capillary loss precedes the cognitive impairment induced by fractionated whole-brain irradiation: A potential rat model of vascular dementia. *J Neurol Sci.* 2007;257(1):67-71.

29. Shin M-H, Kweon S-S, Choi J-S, et al. The effect of an APOE polymorphism on cognitive function depends on age. *J Neurol.* 2014;261(1):66-72.

30. Villasana L, Acevedo S, Poage C, Raber J. Sex- and APOE Isoform-Dependent Effects of Radiation on Cognitive Function. *Rad Res.* 2006;166(6):883-891.

31. Correa DD, Satagopan J, Martin A, et al. Genetic variants and cognitive functions in patients with brain tumors. *Neuro Oncol.* 2019;21(10):1297-1309.

32. Lamborn KR, Chang SM, Prados MD. Prognostic factors for survival of patients with glioblastoma: recursive partitioning analysis. *Neuro-oncology.* 2004;6(3):227-235.

33. Masui K, Cloughesy TF, Mischel PS. Review: molecular pathology in adult high-grade gliomas: from molecular diagnostics to target therapies. *Neuropathol Appl Neurobiol.* 2012;38(3):271-291.

34. Johnson D, Wefel J. Relationship between cognitive function and prognosis in glioblastoma. *CNS oncol.* 2013;2:195-201.

35. van den Bent MJ, Wefel JS, Schiff D, et al. Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. *Lancet Oncol.* 2011;12(6):583-593.

36. Gehring K, Stuiver MM, Visser E, et al. A pilot randomized controlled trial of exercise to improve cognitive performance in patients with stable glioma: a proof of concept. *Neuro-oncology.* 2020;22(1):103-115.

APPENDIX II

List of publications

Van Oostrom I, van Eijndhoven P, Butterbrod E, van Beek M, Janzing J, Donders R, Schene A, Tendolkar I. Decreased Cognitive Functioning After Electroconvulsive Therapy Is Related to Increased Hippocampal Volume: Exploring the Role of Brain Plasticity. *J ECT*. 2018;34(2):1. doi:10.1097/YCT.0000000000000483.

Butterbrod E, Gehring K, Voormolen E, Depauw P, Rutten G, Sitskoorn M. Cognitive functioning in patients with nonfunctioning pituitary adenoma before and after endoscopic endonasal transsphenoidal surgery. *J Neurosurg*. 2019; 133(3):1. doi: https://doi.org/10.3171/2019.5.JNS19595.

Butterbrod E, Bruijn J, Braaksma M, Rutten G, Tijssen C, Hanse M, Sitskoorn M, Gehring K. Predicting disease progression in high-grade glioma with neuropsychological parameters: the value of personalized longitudinal assessment. *J Neuro-oncol*. 2019; 144(3):511–518. doi: 10.1007/s11060-019-03249-1.

Butterbrod E, Synhaeve N, Rutten G, Schwabe I, Gehring K, Sitskoorn M. Cognitive impairment three months after surgery is an independent predictor of survival time in glioblastoma patients. *J Neuro-oncol*. 2020; 149(2): 103–111. doi: 10.1007/s11060-020-03577-7.

Rijnen S, Butterbrod E, Rutten G, Sitskoorn M, Gehring K. Presurgical Identification of Patients With Glioblastoma at Risk for Cognitive Impairment at 3-Month Follow-up. *Neurosurg*. 2020: 87(6):1119-1129. doi: https://doi.org/10.1093/neuros/nyaa190.

Butterbrod E, Sitskoorn M, Bakker M, Jakobs B, Fleuischeuer R, Roijers J, Rutten G, Gehring K. The APOE ε4 allele in relation to pre- and postsurgical cognitive functioning of patients with primary brain tumors. *Eur J Neurol*. 2020 (epub). doi: https://doi.org/10.1111/ene.14693.

Butterbrod E, Schwabe I, Rijnen S, Rutten G, Gehring K, Sitskoorn M. Pre-surgical patterns of cognitive impairment in patients with diffuse glioma revealed by latent class analysis. *Submitted*.

Butterbrod E, Schwbe I, Rutten G, van der Pol B, Rijnen S, Sitskoorn M, Gehring K. Profiles and predictors of cognitive impairment in patients with meningioma before and after surgical resection. *Manuscript*.

APPENDIX III

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